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RECENT ADVANCES IN HÆMATOLOGY

BY

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TO MY WIFE

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PREFACE

THE production of an adequate book dealing with "Recent Advances in Hæmatology" would require an almost encyclopædic knowledge of the vast literature of the subject; and, for my grave deficiencies in this respect, I crave the indulgence of the reader.

I have attempted to give indications of what I regard as being the present position of a number of hæmatological subjects, but have not been able to include every aspect of the science, nor have I been able to make reference to all the investigators who have contributed to our knowledge. I feel certain that, knowing the great difficulties of the task, they will forgive me and realise that only exigencies of space have prevented me from giving them their due. I have realised the defects of this little book so well that, in an appendix, I have given a list of a considerable number of text-books and monographs, which may enable my reader to delve deeper into this fascinating subject. That so many of these books are written in languages other than English can scarcely be reckoned as one of my numerous faults.

My sincere thanks are due to Dr. I. Muende, my assistant, for many valuable suggestions and for much help.

The publishers of the *British Journal of Surgery*, of the *Journal of Pathology and Bacteriology*, of the *American Journal of the Medical Sciences*, of the *Archives of Pathology and Laboratory Medicine*, of the *Proceedings of the Royal Society of Medicine*, and of the *Journal of the Royal Micro-*

scopical Society must be thanked for their kind loan of blocks of illustrations from various of my papers.

I am duly grateful to Messrs. Churchill for their many kindnesses.

Above all, I must thank my wife, to whom this book is dedicated, for her help with the preparation of the index, in the reading of proofs and particularly for her encouragement at times when the preparation of the book was "getting the better of me."

A. PINEY

LONDON,
1927.

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RECENT ADVANCES IN HÆMATOLOGY

INTRODUCTION

Hæmatology has become so very specialised a branch of general biology for a number of reasons, which entitle the subject to separate consideration so long as it is always borne in mind that it cannot be divorced from the general body of biological knowledge.

The circulating blood is, as is universally known, composed of certain formed elements (red corpuscles, leucocytes and thrombocytes or blood platelets), which float in a complex fluid known as the plasma. The phenomena occurring in the plasma and in the fluid left by its clotting (serum) are extremely complicated and do not fall within the purview of the present book; they are the subject-matter of serology, which, nevertheless, usually devotes itself mainly to the study of changes in the serum during and after immunisation.

We have to deal with the formed elements of the blood, which are cells or parts of cells derived from parents situated in certain formative organs of different types. We must, therefore, include in our study the investigation of the characters of the parent cells and the factors influencing the development of the normal formed elements of the blood. This must be an essential preliminary to the study of pathological changes both in the blood and in the formative tissues. Morbid changes can be discussed in one of two ways, viz., as examples of general laws governing blood-formation or as evidences of the effect of some particular morbid stimulus. We shall find it convenient to discuss these two

aspects separately, and it is obvious that, in a sense, they correspond with the conception of general and special pathology of the blood.

The fact that the formed elements of the blood are not developed in the circulation, but are derived from the activities of parent cells in various organs makes clear the error of the conception of the blood as a special form of connective tissue with a fluid matrix; it is really in the nature of a mixed secretion of a variety of origins.

The circulating leucocytes are quite easily distinguishable into two main types, viz., those containing granules in their cytoplasm (granulocytes) and those from which such structures are absent (lymphocytes). In the normal adult body, it is possible to find evidence of formation of granulocytes only in the bone marrow, and, even here, it is localised to special parts of the skeleton. Lymphocytes, on the other hand, can be found in process of development in widely scattered organs (lymphatic glands), and also in small foci embedded in all sorts of organs and tissues. It is very striking that one does not find development of lymphocytes in the normal bone marrow nor is production of granulocytes found in lymphatic tissue. One is led to the tentative conclusion that, although both these tissues contribute to the complement of cells in the circulating blood, they are of entirely different nature. We shall find that the embryological history of the two tissues is quite dissimilar, as is also their response to various physiological and pathological stimuli.

It will be necessary to consider the characters of the parent tissues of the blood cells, and to determine whether they are all of the same origin in the embryo, and whether any common formative tissue persists in post-natal life.

The response of the hæmatopoietic tissues to a great variety of unusual stimuli is manifested by a multiplicity of reactions, and it is possible to make certain generalisations of both practical and theoretical significance. An attempt

at the elaboration of certain general principles will be found in the last chapter of the book.

Unfortunately there are numerous hæmatopoietic reactions whose cause is still uncertain, and, in addition, there are neoplasms of the blood-forming tissues, which, like other new growths, are of unknown ætiology. In spite of this grave defect in our knowledge, it must be our task to attempt to understand the histogenesis of the growths and the mechanism by which they induce changes in the blood.

The methods of morphological hæmatology, which have now reached a very considerable degree of refinement, are of two main classes, viz., quantitative and qualitative. The great essential of every hæmatological investigation is the determination of the number of each kind of formed element in a given volume of blood, but little advance can be made if one does not, at the same time, make a careful study of the nature of the circulating elements. Further, a study of the formative organs must be made a part of the routine whenever it is possible.

In the first appendix of this book, there will be found a number of methods of examining the circulating blood, and, in every complete examination, these should all be included.

Briefly, we may state that hæmatology is that branch of general biological science which deals with the morphology of the blood and blood-forming tissues, but, like every other primarily morphological subject, it requires amplification by data of other branches of knowledge, *e.g.*, chemical and serological.

As a purely descriptive science, hæmatology seems to present no immediate possibility of striking advance unless new technical methods are elaborated, but the possibility of experiment is practically endless, because almost every conceivable manipulation results in more or less important changes in the circulating blood and, therefore, in the hæmatopoietic tissues. It must be realised that the practical exhaustion of one aspect of hæmatological work does not,

in any way, imply that the cultivation of the subject from a slightly different aspect does not offer the chance of well-marked advance. There is now a great body of facts available, and the task before us is the attempt to weld the isolated data into a comprehensible whole.

CHAPTER I

THE RETICULO-ENDOTHELIAL SYSTEM

The term reticulo-endothelium or reticulo-endothelial system is now in very common use, but it seems that there is still a certain amount of uncertainty as to its exact meaning.

In 1899, Ranvier described certain branched cells with oval nuclei, which he had found in connective tissue generally, but particularly in the milky spots of the omentum; these elements were termed "clasmatocytes." He imagined that these cells were modified hæmic leucocytes, and attributed to them both active phagocytic and food-carrying powers. Marchand was able to show that these cells were not modified leucocytes, but are true constituents of connective tissue, mainly of vascular adventitial walls. He referred to them as "leucocytoid cells" because he was able to observe that, in inflammatory conditions, they became converted into macrophages and even into other forms of leucocytes.

The view that these cells are derivatives of embryonic mesenchyme is now no longer disputed, and Marchand's observations have been accepted as demonstrating their truly histioid nature. It was not, however, clear whether these widely-scattered cells were to be regarded as specific differentiations of the mesenchyme or whether they were in the nature of undifferentiated or partly differentiated mesenchymal depôts persisting in post-natal life. If the latter were the case, one would expect that evidence of further elaboration would occur in suitable circumstances; and such an idea is supported by Marchand's observation of their conversion into various types of leucocyte.

The phagocytic activities of these cells are very well marked, but cannot alone be regarded as sufficient evidence for their inclusion in a " system " because it is well known that almost any type of cell can become phagocytic if suitably and sufficiently stimulated.

The true inter-relationships of these scattered cells could be determined only after Ehrlich had introduced various new dye-stuffs. Goldmann showed that these cells all possessed the power of taking up particles of pyrrhol-blue and of certain other stains from the circulating blood.

Briefly it can be stated that these cells are capable of picking up certain colloidal particles in finely granular form ; and so the first demonstration of a functional unity of these scattered cells was obtained. This capacity for storage distinguishes these cells from the other connective tissue elements as well as from all forms of myeloid and lymphatic cells.

As has been stated, vigorous stimulation with suitable substances will result in the development of phagocytic powers in many cells other than those under discussion; and, therefore, it is essential to include only those with a primary avidity for the substance as belonging to this system ; cells which become pigmented only if the dye is in great concentration and after many injections are not necessarily of this type. In the strict sense of the term we can include many of the cells of the splenic pulp, of the medullary follicles and " cords " of the lymphatic glands and of other lymphatic structures, of the splenic sinuses, of liver capillaries (stellate cells of Kupffer), of capillaries in the formative bone marrow, and of the adrenal and pituitary.

The particles are found not only in such cells as are usually called " endothelial," but also in the elongated reticular cells, which, in these situations, are associated with them ; we can, therefore, justifiably include these two types of element together under the name " reticulo-endothelium."

These cells have an extraordinary power of regeneration

after injury, and this fact tends to invalidate all those experiments, which have been designed to elucidate their function by filling them up with some dye-stuff or with Indian ink. It seems proved that it is impossible to cause ablation of the function of a sufficient number of these cells by such means. Further, it appears certain that not all the cells are performing the same function at the same time, because Schittenhelm states that if an animal is injected with two sorts of dye-stuff, some of the cells will contain the one, and some the other, while cells containing granules of both types are very scanty.

The abstraction of dye-stuffs from the circulation is, of course, only an experimental phenomenon, but its occurrence must obviously throw light on certain processes occurring in the normal body. It must be realised that the disintegration of red corpuscles will be followed by the passage of their contained hæmoglobin into solution. Such a solution will, therefore, contain an electro-negative colloid of a kind capable of being dealt with by the reticulo-endothelium. Furthermore, it is quite common to find reticulo-endothelial cells in the splenic pulp in which remnants of degenerate red corpuscles can be recognised; this is surely indicative of the importance of this system in the normal metabolism of the blood. Around extravasations of blood, it is usual to find many cells in which ferruginous pigment is present, although no red corpuscles are recognisable in them; it seems certain that such a condition results from the taking up of diffused hæmoglobin by reticulo-endothelial cells in exactly the same way as they would have dealt with an injected dye-stuff. It is mainly, but not only in the cells of the splenic pulp that erythrophagocytosis can be observed; the Kupffer cells of the liver and the lining of the vascular channels of the marrow also show signs of being actively engaged in blood destruction; and indeed seem to take the place of the spleen in this connection if that organ is removed. It is obvious that such destructive functions must be of great

importance in the regulated process by which the number of red corpuscles in the body is kept at a practically constant level. If we accept the statement of Rich that altered hæmoglobin is the only source of bilirubin, we have also to presume that the importance of the reticulo-endothelial system in the formation of bile pigment is very great.

Although the vexed question of bile formation is not a hæmatological subject in the strict sense of the term, it is very necessary that some description be included at this point because the need for such a summary will be felt when the subject of acholuric jaundice is discussed in a later section.

The classical experiments of Minkowski and Naunyn, who were unable to cause jaundice by arseniuretted hydrogen poisoning in hepatectomised geese, seemed to establish the purely hepatogenic origin of bile pigment. Removal of the liver naturally included removal of the endothelial cells within it, and, as the liver is the main site of reticulo-endothelium in birds, this has to be taken into account in explaining their results. Lepehne stated that, if the reticulo-endothelial cells of the body (naturally including those of the liver) were filled with collargol, there was very appreciable diminution in the amount of bile formation; although his experiments have been widely criticised, they have formed the starting point of many other investigations.

The problems are numerous, but the most striking ones are: Do the liver cells act only as excretory organs for bile, which has been fully formed elsewhere? Do they function as depôts in which the final elaboration of partially prepared bile takes place? Or do they really elaborate the bile from unaltered hæmoglobin? This is obviously not the place to enter into the details of the discussion, important though they are. The demonstration of phagocytic power on the part of the reticulo-endothelial cells suggests that the liver cannot be the only bile-forming organ; and the power of taking up hæmoglobin from solution possessed by these cells

supports this view. Further, there is good evidence that liver cells cannot take up unaltered hæmoglobin. If a small dose of hæmolytic poison be injected into an animal, no hæmoglobinæmia or hæmoglobinuria will result, but histological examination will show the presence of ferruginous pigment in widely scattered reticulo-endothelial cells. If a similar experiment be performed on an animal, which has first had several injections of a suitable dye or preferably of Indian ink, it will be found that hæmoglobinæmia and hæmoglobinuria will result, while no ferruginous pigment will be found in the reticulo-endothelial cells of the body. Further, although the liver cells do not contain much Indian ink, they show no signs of having abstracted any of the liberated hæmoglobin from the circulating plasma. Obviously the liver cannot play the sole part in the metabolism of hæmoglobin.

In animals deprived of their livers a considerable amount of bile pigment appears in the blood plasma after injections of hæmoglobin. If the animal survives sufficiently long after the operation, bile pigment appears in the plasma spontaneously. No clearer demonstration of the occurrence of extra-hepatic bile formation can be imagined.

It must not be supposed that the reticulo-endothelium is exclusively a bile-forming tissue; it has numerous other powers. The first observations on its power of storing fatty materials were made on human tissues in cases of lipoid-æmic diabetes (see p. 212). Kusunoki is of opinion that, even normally, " endothelial " cells of the spleen take part in fat metabolism by dealing directly with both circulating and locally formed fat. Whether this is the case or not, there seems to be no doubt that the number of lipoid-containing cells in the spleen and the lipoid content of the blood serum appear to vary in direct proportion.

Such views are also supported by the observations of Anitschkow, who showed that, if animals are fed on a diet very rich in cholesterol, there results a histological picture

in the spleen, which closely resembles that seen in lipoidæmic diabetes.

A different but confirmatory aspect of the subject has been recorded by Eppinger, who states that splenectomy is always followed by an increase in the amount of cholesterol in the blood. It would be difficult to find any explanation for this occurrence if one did not admit the participation of the spleen in the metabolism of this substance.

Many of the histological features of the spleen of cases of lipoidæmia can be reproduced by the administration of a diet rich in protein (Kuczynski), but here, of course, the stored material is essentially albuminous in nature.

The cells in which the stored material is seen are much larger than normal, but different substances seem to exert varying degrees of stimulation so that storage does not always cause the same amount of cellular over-growth.

Gaucher's disease, which is described in detail later (p. 202), is an example of storage of some unknown material in reticulo-endothelial cells (Fig. 1); and the result is that the cells become enormously larger than normal. The most notable changes are seen in the spleen, but other parts of the reticulo-endothelial system are also involved; for example, there may be so great an overgrowth of the characteristic cells in the bone marrow, that spontaneous fracture may occur (Zadek).

Silver impregnation of sections of the affected organs shows that the Gaucher cells are in the closest possible relationship with very fine argentophile fibrils, whereas the ordinary vascular endothelium of the part is not involved in the process; in this way we get definite evidence of the reticulo-endothelial nature of the characteristic cells.

That there is a close similarity between Gaucher's disease and lipoid hyperplasia is obvious when it is remembered that one of the characteristic accompaniments of the former is the occurrence of yellowish tumour-like masses, particularly on the conjunctiva. These growths are histologically

characterised by the presence of fatty material lying inside reticulo-endothelial (pseudo-xanthomatous) cells; thus, although the material stored in the Gaucher cells of the blood-forming organs is protein in nature, there is clearly a generalised tendency of the reticulo-endothelial tissue to excessive storage of other substances.

It is not possible to determine whether Gaucher's disease

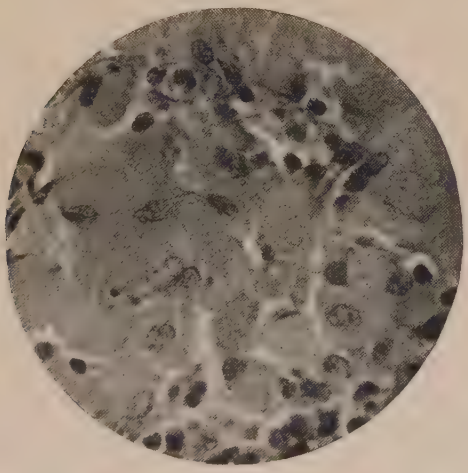

FIG. 1.—Spleen from case of Gaucher's disease (× 640). (From "The Importance of Hæmatology in Surgery." A. Piney. *Brit. Journ. of Surgery*, 1926, xiv.)

The large, finely fibrillated cells, which practically obliterate the normal arrangement of the splenic tissue, characterise the histological picture.

is to be regarded as an inborn error of protein metabolism with consequent storage of abnormal protein metabolites, or whether it is a congenital peculiarity of the reticulo-endothelial system, which has an abnormally great power of storage.

There have often been suggestions that the reticulo-endothelial system is the site of formation of various protective anti-substances, but this has never been satisfactorily

demonstrated. The failure to obtain decisive results is doubtless due in part to the impossibility of completely ablating the function of the cells and so reducing the formation of these substances. There is, nevertheless, some evidence of participation of this system in the processes of immunity. If an animal be injected with a small dose of bacteria, and with a second dose on the following day, there is found to be an enormous and rapid phagocytosis of the injected bacteria by reticulo-endothelial cells.

Some of the most interesting and recent observations relate to pathological overgrowths of reticulo-endothelial tissue. Such conditions as Gaucher's splenomegaly and lipoid-cell hyperplasia have already been mentioned, but hyperplasias of unknown origin also occur. Tuberculosis of lymphatic glands occasionally takes the form of replacement of the gland tissue with " epithelioid " cells, which have been shown to be really reticulo-endothelial (Sabin). More rarely an almost systematic overgrowth of reticulo-endothelium occurs in association with a leukæmic blood picture in which the predominating cell-type is the monocyte (large hyaline leucocyte) (see p. 46).

Aleukæmic proliferations of the system may also occur, and may affect mainly the " endothelial " or the reticular components. Goldschmid and Isaak described the first type of condition in a woman, aged fifty-four, in whose liver, spleen and marrow there was intense proliferation of large endothelial cells. Letterer described a case with the course of an infective purpura in a child, aged six months. Practically all the lymphatic organs were extensively replaced by large cells of various shapes, but all showing close connection with the plentiful reticular fibrils.

The question of the exact relationship of the " endothelial " cells to the reticular fibrils is a difficult one, but Corner has illuminated the subject by showing that it is possible to demonstrate the presence of extremely fine intra-cellular fibrils in the " endothelial " cells; these cytoplasmic

differentiations emerge from the cells and pass out to form a fine network in the inter-cellular spaces. We have now, therefore, a morphological criterion of the reticulo-endothelium.

The existence of true blastomatous neoplasms of the reticulo-endothelial system can obviously be determined only if a morphological feature is available for recognition; this

FIG. 2. –Intra-cellular fibrils in reticulo-endothelial cells. (Reprinted from "Endotheliomas: with Special reference to those growing in Solid Form." A. Piney. *Archives of Pathology and Laboratory Medicine*, 1926, ii.)

The drawing illustrates clearly the morphological justification for the use of the term "reticulo-endothelium."

must be taken to be the formation of fibrils as described by Corner. The first case of definitely recognisable reticulo-endothelioma was described by Foot, but his conclusion as to its nature was based on inference rather than on observation of this morphological peculiarity. I have been able to show that, in some "endotheliomata" there is formation of intra-cellular fibrils similar to the condition described as being normal by Corner (Fig. 2). We have, however, no

knowledge of either blood formation or destruction by the cells of such tumours.

The hæmatopoietic functions of the reticulo-endothelial system fall to be discussed in the next chapter, and, from the present point of view, are its most important activities; details of the metabolic and blood-destroying powers can be found in Aschoff's critical review of the subject.

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CHAPTER II

THE DEVELOPMENT OF BLOOD CELLS

The fact that blood cells continue to develop in large numbers in post-natal life as well as before birth, makes it obvious that the two modes of development must be considered in one section of this book; and it is convenient to travel backwards from the mature circulating cells to the more primitive forms in the present account.

The most noticeable feature of a film preparation of stained blood is that, while all the red corpuscles are identical, the nucleated elements fall into two main classes, viz., those that contain true cytoplasmic granules and those that have no such differentiations.

The granular leucocytes require separate discussion. The neutrophilic polymorphonuclear leucocyte with its very characteristic nucleus does not form the whole complement of neutrophilic granular cells in normal blood; about 4 per cent. of cells containing these granules have an unlobed, but bent, nucleus. These are metamyelocytes, and represent a stage in the development of the polymorphonuclear cell. In the bone marrow, and also in the blood in pathological conditions, a mono-nuclear cell with neutrophilic granules can be found in large numbers; this is the myelocyte or fully granular precursor of the metamyelocytes and polymorphonuclears. There appears to be no doubt that it is derived from an incompletely granular cell known as the premyelocyte. This is a mono-nuclear cell with faintly basophilic protoplasm and many neutrophilic granules in its cytoplasm, although the number is not so great as in the more mature forms. Nucleoli may be visible in the nucleus. Normally the

greater number of granulocytes arise, in post-natal life, from division of myelocytes, and not by differentiation from less mature forms. The premyelocyte is developed from a non-granular ancestral cell commonly known as the myeloblast; this type forms one of the subjects of discussion in the present chapter (see Plate I.).

The eosinophilic polymorphonuclear leucocyte has an ancestral history identical with that of the neutrophilic granular cells, but it is important to recollect that, although the mature granules have a great affinity for eosin, the younger ones do not show this property, but are indulinophile; they may be seen in the less mature types of eosinophilic granular cells, and may even be mistaken for basophilic granules.

The basophilic granular leucocyte is also polymorphonuclear and has a similar developmental history, but its granules have a basophilic reaction throughout.

The large hyaline leucocyte or monocyte is not easy to place with certainty into either the granular or the non-granular group. The cells have finely-drawn nuclei and faintly basophilic cytoplasm in which are cherry red granules (*azur granules*) in the mature forms of the cells. The nucleus may be smoothly oval or indented (transitional leucocyte of Ehrlich). The origin of these cells is discussed later, but here it can be stated that the younger forms have few or no granules, and may show the presence of nucleoli in the nucleus.

The lymphocytes are the typically non-granular leucocytes; they may be large (with a comparatively large amount of protoplasm) or small (with the merest rim of protoplasm). The nucleus is usually round or only slightly indented, and is characterised by very indistinct differentiation of basi- from oxy-chromatin. Azurophilic particles of irregular shape and size may sometimes be seen in the protoplasm of large lymphocytes, particularly in children; these are much larger and more irregular in shape and occurrence than the

true azur granules of the monocyte. The large lymphocyte is not necessarily younger than the small form ; the criterion of immaturity is to be sought in the characters of the nucleus. The nucleus of young lymphocytes is less dense, and nucleoli may even be present ; this cell is often known as the lymphoblast ; a discussion of its nature will be found later.

The red corpuscles are derived from nucleated precursors (normoblasts), which, in their younger stages, show a " cart wheel "arrangement of the nuclear chromatin. The normoblast is but little larger than the mature red corpuscle, but its very early stage, which is hardly at all hæmoglobiniferous, is much larger (macro-normoblast), although the cart wheel arrangement of the nucleus is always present.

The blood platelets (thrombocytes) are small non-nucleated elements with a collection of minute azurophilic granules at their centre. Although they are invariable constituents of normal blood, their origin is still uncertain. A view which has found and still finds much favour is that of Wright, who states that they represent portions of the separated cytoplasm of megakaryocytes in the bone marrow. This theory is supported by the morphological resemblances between the protoplasm of the megakaryocytes and that of the thrombocytes, but recent work has cast much doubt on the validity of Wright's interpretation (see later).

The progress of hæmatology has been much impeded by an old and persistent controversy as to the origin of the blood cells. There are two main schools of thought on the subject. The adherents of the one view contend that all the blood cells are derived from a common ancestor, which persists in post-natal life, *e.g.*, although lymphatic organs usually produce only lymphocytes, they can, in altered circumstances, produce granulocytes and red cells on account of the persistence of the stem cell. Some members of this monophyletic school go so far as to contend that this common ancestral cell, which they know as the lymphoidocyte or hæmocytoblast, persists in post-natal tissues, and can appear in the circulating blood

in pathological conditions. The other school is of opinion that the common ancestral tissue disappears before birth, leaving only myeloid and lymphatic stem cells to carry on the process of hæmatopoiesis in post-natal life. Some would contend that the red cells and granular leucocytes are developments of the myeloid stem cell, but others presume that the red cells have a separate ancestor. An extension of this dualistic view is that of Aschoff and Kiyono that the monocytes are derived from a third hæmatopoietic tissue (reticulo-endothelium).

Any account of the development of the blood cells will naturally have to contend with the difficulty of interpretation in the light of these widely differing hypotheses, but, while attempting to attach due value to the recorded observations, I can scarcely avoid emphasising my own opinions.

In the discussion of the first appearance of blood cells in the embryo, we meet with the greatest difficulty inasmuch as some observers (Maximow) state that the blood islets on the wall of the yolk sac are of purely mesenchymal origin, while others (Lenaz, Duval) state that they are entodermal. The latter view is certainly supported by the fact that, at the time of earliest blood formation, there are no formed organs in the embryo and, therefore, transport of the yolk substances is very essential. Maximow states that the blood islets are solid masses of primitive mesenchyme in which the central cells become free as primary blood cells (hæmocytoblasts), while the peripheral ones remain as an endothelial wall. The adherents of the view that the primitive blood is entodermal contend that the entodermal masses become surrounded by mesoblastic endothelium, which, therefore, takes no part in this form of hæmatopoiesis. It is very striking that this extra-embryonic form of hæmatopoiesis is later seen in the liver of the embryo (*vide infra*). Maximow states that these first formed blood cells are the ancestors of all the types that develop later, but some writers (Schridde, Piney) contend that they are all hæmoglobiniferous elements.

Maximow's description implies that some of these primitive cells become hæmoglobiniferous and act as temporary carriers of oxygen (primitive erythroblasts), while the others retain all their hæmatopoietic potencies. Lenaz, Schridde, and Piney also regard these first formed cells as having only a short life in the embryo, but consider that they are all nucleated red cells (megaloblasts), which normally persist longest in the liver of the embryo from which they disappear before birth. Ferrata, di Guglielmo, and Lambin, although believing that the islet cells are multi-potent, state that the first brood of these cells all become bearers of hæmoglobin.

There is no doubt that there develop certain amœboid cells from or near the primitive endothelium (Sabin); Ferrata and his followers state that all the white cells of primitive blood in the embryo are of such endothelial origin (hæmohistioblasts), *i.e.*, are not derived from the first formed intravascular islet cells. This would seem to be the first sign of appearance of a reticulo-endothelial or histiocytic tissue in the embryo, and would supply an explanation of the appearance, in the liver, of both intra- and extra-vascular foci of hæmatopoiesis.

The embryo is thus supplied, for a short time, with two varieties of blood; one derived from the entoderm, and composed purely of hæmoglobiniferous cells; and the other of mesenchymal origin, and consisting of both red and white cells. The main mesenchymal mass of the embryo consists of fixed cells, together with a variable number of wandering cells of monocytic type. The majority of the fixed cells differentiate irreversibly into fibroblasts, *i.e.*, collagen-producing cells, while a portion remain in an undifferentiated condition as a reservoir of fibroblastic and hæmatopoietic potencies throughout life. These cells may be difficult to distinguish as they lie between other connective tissue elements, but vital staining demonstrates their position and storing capacities. These cells are the resting wandering cells of Maximow, the macrophages of Evans, the rhagiocrine

cells of Renaut, and the clasmatocytes of Ranvier. In the hæmatopoietic tissues proper (bone marrow, spleen, etc.) they form continuous masses closely connected with the fibrillar reticular framework of these organs. From the account given in Chapter I. it is clear that this is the reticulo-endothelial system (hæmohistioblasts of Ferrata).

The adherents of the monophyletic view contend that this histiocytic or reticulo-endothelial system can, at any time during life, produce hæmocytoblasts with the power of developing into any type of blood cell.

There is no doubt that, in normal extra-uterine life, new blood cells develop mainly on the so-called homoplastic plan (Ellermann), *i.e.*, each cell type arises by division of another of the same sort so that myelocytes (and, therefore, polymorphonuclears) develop from the products of division of other myelocytes; development from a more primitive ancestor is a rarer and more usually, in adult life, a pathological phenomenon.

The polyphyletic school contends that there is a myeloid and a lymphatic stem cell; the myeloblast and the lymphoblast respectively. These may, of course, be derived from such a reticulo-endothelial tissue, but have a fixed myeloid or lymphatic potentiality immediately they develop. There are, however, monophyletists (Downey), who, while not admitting the validity of this view, state that the hæmocytoblast (multi-potent offspring of the reticulo-endothelium) almost immediately shows morphological differences between myeloid and lymphatic stem cells. It is stated, by the monophyletists, that myeloid or lymphatic tissue respectively will arise from the reticulo-endothelium according to the chemical environment of the tissue at the time, *i.e.*, different circumstances will result in the development of different types of cells; it would seem, therefore, highly improbable that altered environment would not alter the stem cell itself immediately. It appears, thus, perfectly justifiable to accept the existence of at least two stem cells, even while admitting

that they take their origin in a common partially differentiated reticulo-endothelium.

We are still left with a difficulty with regard to the monocytes ; they, like the other blood cells, are derivatives of the reticulo-endothelium, but the question as to whether they arise directly from it or from either the myeloblast or the lymphoblast remains to be discussed. I (1926) have attempted to make certain distinctions between myeloid and lymphatic cells on purely morphological grounds ; it was found that all the typical granular leucocytes show a well-marked distinction between the nuclear oxy- and basichromatin, whereas lymphatic cells show an ill-defined edge between the two substances, giving the impression of the presence of continuous diffusion processes between them. Similar criteria can also be made use of in distinguishing the non-granular precursors ; thus, the myeloblast shows a much finer stippling of the nucleus than does the lymphoblast, whereas that of the latter is definitely coarser (Plate I., Fig. II.). The mature monocyte has the typically myeloid arrangement of the nuclear constituents, and, further, all varieties of morphological transition between the myeloblast and the monocyte can be found (Plate I., Fig. III.). These transitional forms should be termed pro-monocytes (Hittmair), rather than monoblasts (Ferrata), as the latter term suggests that these cells have a line of development as distinct and separate as that of the myeloid and the lymphatic cells. We can, therefore, accept the contention of Aschoff and Kiyono that the monocytes are derivatives of the reticulo-endothelial tissue, but only by the intermediation of the myeloblast, *i.e.*, the monocyte is as much a myeloid cell as is any other granular leucocyte.

Before continuing the account of hæmatopoiesis, it would be well to adduce experimental evidence of the hæmatopoietic function of the reticulo-endothelium. Elvidge has shown that intra-venous injections of quartz particles, which are picked up by reticulo-endothelial cells, result in the pro-

duction of very striking modifications of the circulating blood. Single injections are followed by the appearance of large numbers of nucleated red cells in the circulation, although there is no concomitant anæmia ; this represents a so-called " blood crisis," such as is seen in human pernicious anæmia. Repeated injections result in the development of anæmia together with " blood crises." Similar changes occur after injection of other particles, *e.g.*, carmine, Indian ink, which are known to be stored by reticulo-endothelial cells. The " blood crisis " disappears long before the cells have ridded themselves of the particulate material, thus demonstrating the great power of regeneration of this system. Here we are dealing with a direct effect upon the reticulo-endothelial system, and there can thus be no doubt of its importance in hæmatopoiesis (see also under " Myeloid Metaplasia ").

The account of blood-formation inside the body of the embryo can now be continued. The type of hæmatopoiesis which occurs on the yolk sac continues in the liver of the embryo, and, as would be expected from our knowledge of the condition in the yolk sac, is intra-vascular in position. The process results in the formation of red cells only, from which non-nucleated red corpuscles of large size arise. This process of pure erythropoiesis is soon supplemented by the appearance, in peri-portal tissues, of collections of other blood cells ; these are of various types, viz., non-granular mono-nuclear cells with the morphological characters of myeloblasts, granular leucocytes, and red cells with " cart wheel " nuclei (Fig. 4). This second type of blood formation represents an intra-hepatic, but partly extra-vascular, production of all the cell types, which occur in normal bone marrow. The intra-lobular nucleated red cells show no sign of a cart wheel arrangement of the nucleus, and, in fact, have no genetic relation with the red cells formed in the peri-portal spaces ; the former are entodermal, the latter mesodermal in origin.

The intra-vascular mechanism for the production of the

primitive blood undergoes gradual atrophy while the secondary hæmatopoietic tissue becomes hyperplastic and

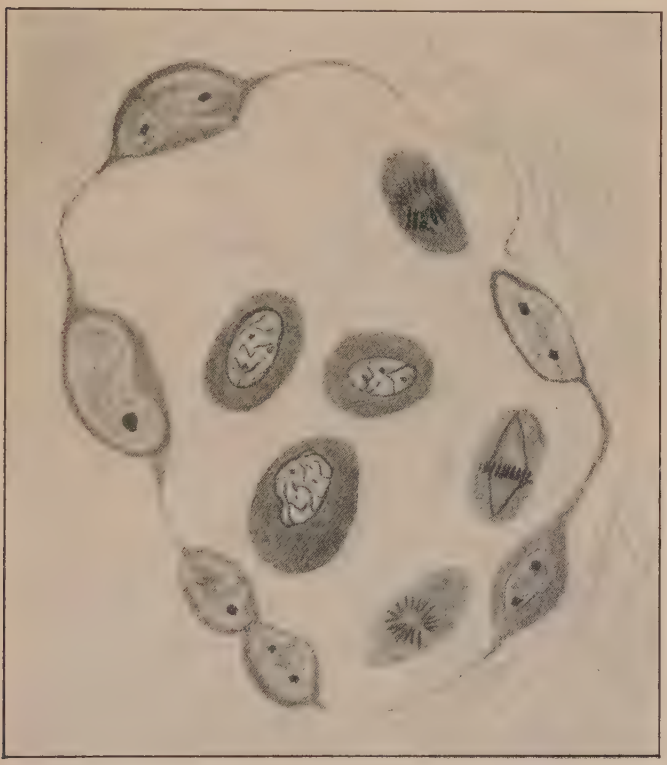

Fig. 3.—The section shows a blood island from the yolk sac of a human embryo. The lining cells forming a series of fused cells are seen to bound a cavity in which lie six cells of which three are in process of mitotic division, while three are in a resting stage. The latter three are drawn so as to show the essential characters of the nuclei, which are very different from those of the lining ("endothelial") cells. No evidence is here adduced of derivation of the free cells from the "endothelial" ones, and, throughout this book it is contended that the two groups are of entirely different origin and functional abilities. (Reprinted from "Some Morphological Factors governing the Incidence of Pernicious Anæmia." A. Piney. *Proceedings of the Royal Society of Medicine*, 1925, vol. xviii. (Section of Pathology), pp. 5 to 9.)

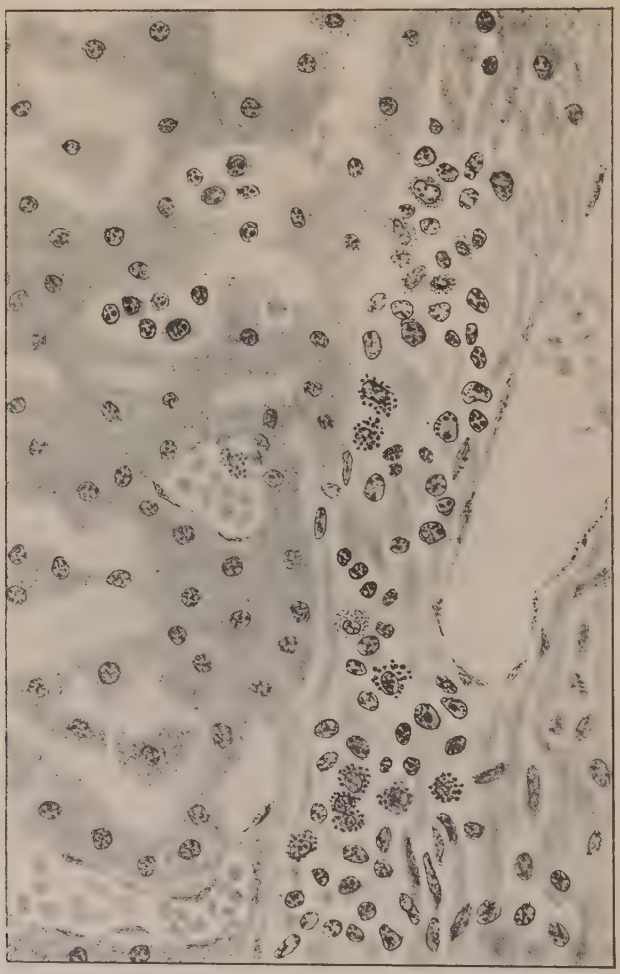

FIG. 4.—The section shows a portion of the liver of a human embryo (fifteen weeks). In the right-hand part of the picture is seen a portal tract in which both granular and non-granular cells are present; some of the former can be seen to have "cart wheel" nuclei and so to possess the characters of normoblasts. In one of the capillaries to the left-hand side of the middle of the picture is seen a small group of cells in which the characters of normoblasts are absent and no granules are visible; these are the megaloblasts, which represent an intra-embryonic exten-

is gradually transferred entirely to the bone marrow; the primitive mechanism cannot normally be found in the liver or elsewhere in the body at birth.

Lymphocytes develop in follicles which are formed in connection with lymphatic channels.

A brief summary may be convenient :—

Primitive red blood cells (megaloblasts) develop in the blood islets on the wall of the yolk sac, and later in an intravascular position in the liver. They are of entodermal origin and have no relationship with the later or definitive blood.

Ordinary nucleated red cells (normoblasts), together with granular leucocytes and their precursor (myeloblast), develop in the peri-portal connective tissue, and later in the bone marrow. They are of mesodermal origin, and can arise, in suitable circumstances, wherever reticulo-endothelial tissue is present.

Reticulo-endothelial tissue can give rise to all types of blood cell in differing circumstances, but no common ancestral blood cell (lymphoidocyte) is known. The myeloid stem cell (myeloblast) and the lymphatic stem cell (lymphoblast) can be distinguished from one another by their morphological characters although they both arise from reticulo-endothelium, which is an undifferentiated remnant of embryonic mesenchyme.

The attitude, therefore, to be taken in this book is a modified polyphyletic one.

Before proceeding to a discussion of the origin of the blood platelets, it will be well to describe the condition known as **Myeloid Metaplasia.** This term is applied to the appearance

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sion of the form of hæmatopoiesis occurring on the yolk-sac. The separation of these two types of blood formation is not only a spatial one, but the results of the two processes are essentially different. In the portal tract are formed granulocytes and red cells, *i.e.*, myeloid tissue of the type which later develops only in the bone marrow; while in the capillaries of the liver lobule there develop only red cells with all the characters of megaloblasts, *i.e.*, cells which are absent from the body in normal extra-uterine life. (Reprinted from the same source as Fig. 3.)

and formation of myeloid cells (red cells and leucocytes) in positions from which they are normally absent in extra-uterine life. Such a condition is seen in many severe anæmias and, for this reason, has often been regarded as a compensatory phenomenon. It can, however, occur in the complete absence of anæmia, *e.g.*, as the result of the action of minute doses of various toxins. It can also be caused by any sufficiently long continued stimulation of the reticulo-endothelial system. Lang was able to show that intense myeloid metaplasia could be produced by repeated injections of carmine, *B. coli* vaccines and saponin. He, as a monophyletist, was supported in his views by the fact that the myeloid metaplasia affected even the germ centres of lymphatic tissue. He believes that multi-potent hæmocytoblasts collect in the vessels of the part and give rise to the various types of granular and red cells, which ultimately take up an extra-vascular position. There is, however, good evidence that the process of erythropoiesis is intra-vascular throughout life (Piney (1922), McGowan), while leucocyte formation remains extra-vascular. Lang's conception would thus imply emigration only of leucocytes from the vessels ; his very beautiful illustrations show a much greater number of leucocytes outside the vessels than in the lumen, while all the red cells are intra-vascular. There seems to be little reason to suppose that these are not the original sites of formation of the two types of cells. He very clearly shows the development of granules in the protoplasm of reticular cells, and of hæmoglobin inside similar cells. There is another excellent reason for doubting the intra-vascular formation of both varieties of cells. They are admittedly derived from identical parent cells (reticulo-endothelial cells), and it may surely be presumed that identical cells in identical circumstances can only give rise to one type of offspring. If, however, they give off some cells inside the vascular lumen and some in the other direction, one would expect the resultant daughter cells to be of different types.

It is only in this way that one can explain the development of red cells and granular leucocytes in the same foci. This conception is supported by the fact that the reticulo-endothelial cells of a lymphatic tissue, which have taken on the process of myelopoiesis in their experimentally altered circumstances, cease to perform their previous function of lymphocytopoiesis. Lang's work thus seems to support the modified polyphyletism here advocated.

The origin of the **Blood Platelets** (thrombocytes) is still an unsolved problem. For a considerable period of time Wright's theory, that they represented separated portions of the protoplasm of megakaryocytes in the bone marrow, has held the field. It is, therefore, necessary to describe this peculiar type of cell. The megakaryocyte, as seen in adult bone marrow, is a very large cell with many nuclei, which have apparently all the same structure. Younger forms with less complex nuclei are always present, but are most numerous in embryonic life and in anæmias; these cells (megakaryoblasts of Ferrata) are actively phagocytic, or, at any rate, frequently show the presence of leucocytes in their cytoplasm. The protoplasm contains extremely fine azurophilic granules, except in a narrow zone at the edge. The cells lie in the closest possible proximity with the reticulo-endothelium of the marrow, and appear to be derived from it (Fabris); their apparent power of phagocytosis is, therefore, not surprising. If these cells be not the ancestors of blood platelets (and there seems to be some reason for doubting it), it is necessary to inquire what function they can serve. McGowan has made certain revolutionary suggestions in this connection. He points out that the first formation of blood cells on the wall of the yolk sac is composed of a syncytial mass of multi-potent hæmocytoblasts (the position taken in the present book is, of course, a different one, viz., that these primitive cells are entodermal erythroblasts). McGowan follows Maximow, and Jolly in their view that the megakaryocyte is derived from hyper-

trophy of the hæmocytoblast, but parts from them when they regard the cell as being phagocytic. He supposes that the cells found inside the cytoplasm of the megakaryocyte have entered it on a destructive mission ; the absence of a phagocytic power is rendered conceivable by the experiments of Bedson and Johnston, who were unable to find carmine and Indian ink in these cells after injection. McGowan appears to believe that the protoplasm of the megakaryocyte contains a certain amount of hæmoglobin, and that the blood pigment, which is sometimes found inside it, is a degenerative and not a phagocytic product. It has already been mentioned that Ferrata has shown that leucocytes and other foreign substances are found more commonly and in larger amount in the young megakaryocytes ; this scarcely suggests the probability of destruction of the young cell by invading leucocytes.

Firket and Campos have shown that a well-marked megakaryocyte reaction can arise in association with aplasia of the marrow due to benzol poisoning. McGowan, therefore, suggests that, by amitotic division, the megakaryocyte may give rise to a number of multi-potent stem cells (hæmocytoblasts), and so represent a true regenerative mechanism. If we could accept McGowan's conclusions, it would be clear that the megakaryocyte is an ancestor of the blood platelets only inasmuch as it is capable of giving rise to hæmocytoblasts, which are the true ancestral form of these particles.

Criticisms of Wright's theory have been made by Petri from the experimental aspect. He has adopted various methods of influencing the number of platelets in the circulation, but has not been able to find any relationship between their number and the quantity of megakaryocytes in the bone marrow. He concludes that a megakaryocytic origin is very improbable, but is unable to put forward any other hypothesis. It is clear from the work that has been done that the platelets are certainly not simple precipitations in the plasma, as was long suggested by the physiologists.

The very difficult and controversial subject of the **Origin of the Red Corpuscle** remains to be discussed; it is here possible to do little more than indicate personal views on the subject, while freely admitting that they do not offer a solution of all the problems.

It is obvious that the adherents of the monophyletic school will be of opinion that the red corpuscle is derived from the primitive stem cell (hæmocytoblast). They contend that all sorts of transitions can be found between large non-hæmoglobiniferous cells (pro-erythroblasts) and the mature, fully hæmoglobiniferous corpuscle. It is essential to give an account of the attitude here taken up, while criticising the monophyletic view.

It has already been stated that the first and only cells to appear in the blood islets of the yolk sac are hæmoglobiniferous erythroblasts, which also develop in an intra-vascular position in the primitive liver. These cells have a very finely reticular nucleus and a cytoplasm, which, with increasing maturation, comes to contain much hæmoglobin. The nucleus may be lost from this cell, and the resultant red corpuscle is larger than the ones seen in the normal circulation in post-natal life, but it is well filled with hæmoglobin. This corpuscle is an obvious giant in a morphological sense, but, on account of its excessive complement of hæmoglobin, is also a functional one. The term megaloblast is applied to the nucleated cells of this type, and megalocyte to its non-nucleated giant offspring.

The red cells, which develop intra-vascularly from reticulo-endothelium, in foci common to them and to granular leucocytes, start as large non-hæmoglobiniferous cells with a " cart wheel " arrangement of the nuclear chromatin; at this stage they are larger than normal red corpuscles. Increasing maturation is associated with increase in the amount of hæmoglobin in the protoplasm and decrease in size of both the nucleus and the cytoplasm, *i.e.*, of the whole cell. The large form is known as the macro-normoblast,

and the small one as the normoblast (Piney (3)). In normal hæmatopoiesis the normoblast gradually loses its nucleus (probably by a process of solution in the protoplasm), and gives rise to a fully hæmoglobiniferous corpuscle smaller than that derived from the megaloblast ; this is the normocyte or ordinary red corpuscle. In conditions of unusual demand for red corpuscles, the incompletely hæmoglobinised macro-normoblast may lose its nucleus, but the resulting non-nucleated corpuscle, although a morphological giant, will not be a functional one on account of the defective supply of hæmoglobin ; this is the macro-normocyte.

It is now presumably clear that the megaloblast can, in no circumstances, be regarded as an immature normoblast (quite apart from my view that the former is entodermal in origin, while the latter is mesoblastic), because the megaloblast has a complete developmental history, just as has the macro-normoblast-normoblast series of red cells. If the present account of the embryology of the process be accepted, it will be obvious that the appearance of megaloblasts in post-natal life must always be a pathological condition dependent upon the persistence of some remnant of its entodermal "Anlage." The process of disappearance of megaloblastic tissue in the liver and the concomitant hyperplasia of the normal normoblasto-granulocytic tissue has already been described, and there seems to be but little doubt that these are correlated processes ; therefore, if there is incomplete atrophy of the one tissue, there will be defective formation of the other. We may well expect that the power of producing megaloblasts in post-natal life will be associated with a poor quality of bone marrow in the person concerned (see Pernicious Anæmia, p. 79).

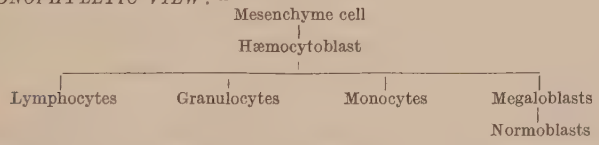
A very *brief summary* may make clearer the position taken up with regard to hæmatopoiesis :—

The first cells to appear in the embryo are of entodermal origin, and are all hæmoglobiniferous ; they are megaloblasts, and are absent from the normal human being in post-

natal life. Later, intra-embryonic hæmatopoiesis takes place by differentiation of reticulo-endothelial cells, which can, according to their environment, produce myeloid or lymphatic stem cells, which are morphologically different cells. The myeloid stem cell is capable to giving rise to nucleated red cells (normoblasts) into the lumen of vessels, and to myeloblasts extra-vascularly. The lymphatic stem cell arises in association with lymphatic reticulo-endothelium. All these cells are mesoblastic in origin.

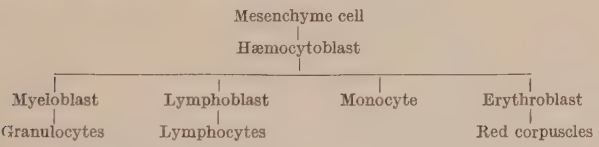
The following charts may make clearer the various views of the process of blood formation :—

MONOPHYLETIC VIEW:—

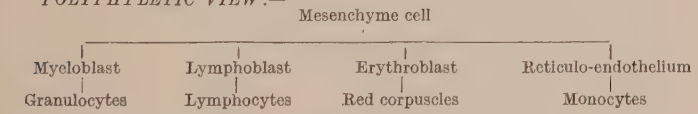


All these cells, with the exception of the mesenchyme cell, are present in post-natal life.

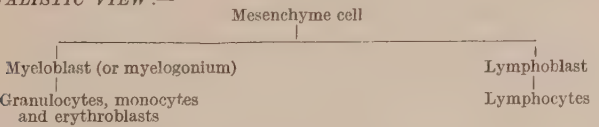
DOWNEY'S MODIFIED MONOPHYLETIC VIEW:—



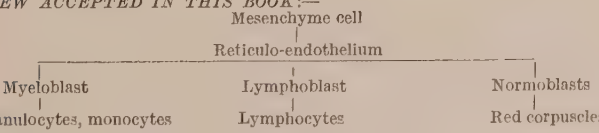
POLYPHYLETIC VIEW:—



DUALISTIC VIEW:—



VIEW ACCEPTED IN THIS BOOK:—



In this system the megaloblast is regarded as a separate cell type derived from the entoderm, and having no representative in normal post-natal life.

Each of these schemes has been reduced to its baldest essential; further information is to be sought in the text.

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CHAPTER III

"LEUKÆMIA"

When Virchow gave his first account of leukæmia, he stated that it was a malady characterised by a progressive and ultimately extreme increase in the number of circulating colourless blood cells. He called transitory states of such hyperleucocythæmia, leucocytoses, but, when they were persistent and progressive, he termed them leukæmia. He did, however, realise that this dyscrasia was not primary in the blood, but was a malady affecting the blood-forming tissues, which to him were the spleen and lymphatic glands. To-day, we have had to give up the older conception of the blood as a special form of connective tissue with a fluid matrix; we have to regard it as a composite fluid containing the products of all the hæmatopoietic tissues. For this reason we have to regard "leukæmia" as a disease of these tissues instead of as a "blood disease"; in fact, the idea of a disease of the blood itself is not tenable.

The changes, which occur in the blood in the "leukæmias," are thus indicative of alterations in the formative tissues, and are seen in the form of changes in the qualitative composition of the circulating fluid. Frequently there is also a quantitative change, but the degree of the leucocytosis is not a diagnostic feature. It has long been recognised (Cohnheim) that all the anatomical changes characteristic of "leukæmia" might occur without any increase in the number of circulating leucocytes, although there were grave alterations in the quantitative composition, as evidenced by the presence of immature white cells of a character not found in the normal circulation; this is the

"pseudo-leukæmia" of Cohnheim, and the aleukæmic leukæmia of many authors. The essential changes in the hæmatopoietic tissues in these diseases are great cellular overgrowth together with alteration in the structure of the newly-formed cells. The suggestion of Orth that all such processes be included under the term *hæmoblastosis* will be adopted here. The essential dissimilarity of the myeloid and the lymphatic tissue has already been described, and it is obvious that such a hæmoblastosis may affect either of these tissues (*myelosis* and *lymphadenosis* respectively).

As the blood cannot reasonably be regarded as a special form of connective tissue, we can no longer speak of "diseases of the blood," but must look in the blood-forming organs for a basis of classification.

Hyperplasia of hæmatopoietic tissue can occur as the result of a very great variety of stimuli, most of which act by imposing a demand for increased cytopoiesis. Such a demand may be due to increased destruction of blood cells in the body, to loss from the body by hæmorrhage, or to the presence in the body of some substance, which is positively attractive to some form of hæmic cell. It is conceivable also that the number of circulating cells might be increased as the result of some primary increase in the size of the hæmatopoietic tissue; such a condition is seen in association with the excessive amount of lymphatic tissue in status lymphaticus, where there is a lymphocytosis in the blood, which can be attributed solely to the abnormally great size of the formative tissue, and not to any demand for an increased number of cells in the circulation.

Increase in the number of circulating cells can occur also if the formative organs become hyperplastic for some reason other than response to increased demand for cells, even if the greater size of the hæmatopoietic organs is acquired and not congenital. The term "hæmoblastosis" can very suitably be applied to all such forms of hæmatopoietic

excess, and these conditions will almost always be accompanied by alterations in the circulating blood.

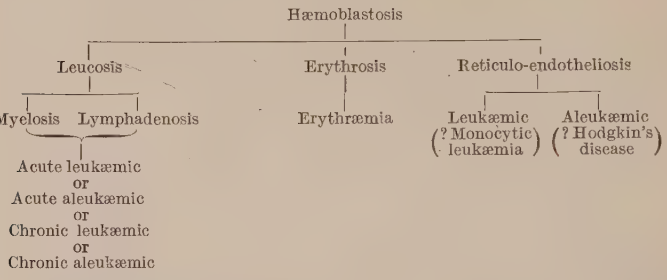
It is possible to make a useful classification of the hæmoblastoses if we bear in mind the essential characters of the various formative tissues. First, we have to recollect the very different nature of lymphatic and myeloid tissue respectively; and, therefore, must sharply separate hyperplasias of the one from those of the other. Lymphatic hyperplasia of the type described above can be called lymphadenosis, while a similar affection of myeloid tissue will be known as myelosis. The name " leucosis " is suitable for all forms, either lymphatic or myeloid, and is much to be preferred to leukæmia, which is, after all, only a name descriptive of a very striking hæmatological sign, but is not, in the strict meaning of the term, always present.

Hyperplasias of a character similar to those occurring in the leucopoietic tissue may affect the erythropoietic one, which is, as has already been explained, a part of the general myeloid system. It is convenient to refer to this condition of hyperplasia, of the red-cell-forming tissue only, as *erythrosis*, and the excessive number of red corpuscles in the circulation forms the symptomatic blood picture known as *erythræmia*. A concomitant hyperplasia of both erythropoietic and leucopoietic tissue can be termed *erythro-leucosis*, or, as both red cells and granulocytes are formed in the bone marrow, as *pan-myelosis*, so indicating that the whole of the myeloid mechanism is affected.

The reticulo-endothelium is the great hæmatopoietic tissue, which produces different types of cells according to its environmental circumstances; therefore, the ordinary forms of leucosis and erythrosis can be regarded as representing errors in the development of the cells derived from the parent reticulo-endothelium, but it is possible that hyperplasias of this ancestral tissue itself may occur, with or without qualitative changes in the characters of its offspring. Such states are best termed " reticulo-endothelioses,"

and may be associated with symptomatic changes in the circulating blood.

It is possible and convenient to summarise these observations in tabular form :—



Chronic Myelosis.—This form of leucosis is, of course, essentially an overgrowth of the myeloid tissue in all the bones, but there is, in addition, usually a well-marked degree of myeloid metaplasia in tissues other than the bone marrow.

The extent of the *bone marrow* varies very considerably at different ages (Piney). At birth all the bones contain red formative marrow, but gradually fatty tissue develops in the medullary cavities of the long bones, and, to a variable extent, replaces the formative tissue. The distal long bones of the adult skeleton contain only fat, and even the proximal ones possess only a very small islet of red marrow at their upper ends. The ribs, flat bones and vertebral column contain hæmatopoietic marrow throughout life, although there is always a considerable microscopic admixture of fat cells. The myeloid tissue, which does not undergo physiological atrophy, retains an enormous power of hyperplasia, which can manifest itself in a very striking manner, even in chronic infections, but is most extensive in cases of myelosis and pernicious anæmia, where the formative tissue may again reach such a size as to fill the bones in the same manner as is normal in infants.

This metaplastic reappearance of hæmatopoietic tissue is not confined to the medullary cavities, but such embryonic

blood-forming tissues as the splenic pulp can again take on the function. Even tissues, which are not actively hæmatopoietic at any stage of ante- or post-natal life can commence to form blood cells ; and this is the basis of the " leukæmic infiltrations," which are found widespread in the organs of sufferers from myelosis, *e.g.*, although rare, nodular infiltrations of the normally non-hæmatopoietic subcutaneous tissue may occur (Zurhelle).

At first sight, it is surprising that such enormous increase of blood-forming tissue is almost invariably accompanied by definite and progressive anæmia. The explanation of the anæmia associated with myelosis seems to be the same as that accompanying chronic infective processes. It has already been stated that the reticulo-endothelial (histiocytic) lining cells of the blood vessels of the bone marrow are the common ancestral tissues of both granular leucocytes and red cells, but the former are produced into the extra-vascular tissues, while the latter are formed towards the lumen. It is possible to stimulate one of these functions with little or no associated increase of activity of the other ; this is well seen in the leucocytosis of infection, which is presumably a direct response to increased demand upon the functional abilities of the leucopoietic tissue. In myelosis, there is also excess of the one aspect of the function of the myeloid reticulo-endothelium, and it seems probable that, both in chronic infections and in myelosis, there is not the ability to perform the one function to excess without, at the same time, interfering with the completeness of the other. It is not surprising to find that, as a rule, the reticulo-endothelium cannot, at one and the same time, produce a normal number of red cells and an excess of leucocytes for long periods of time.

The striking feature of the blood picture of cases of myelosis is the presence of immature forms of granulocytes ; it is unfortunate that we do not know the mechanism that normally controls the emigration of leucocytes from the

marrow, but a possible explanation of the appearances seen in myelosis can be found. The blood vessels of the marrow are composed of histiocytes (reticulo-endothelium), and the leucopoietic process occurs on the outer aspect of these boundaries; it may well be supposed that any injury to the vascular walls will permit immature leucocytes to escape into the lumen and so reach the general circulation. The vascular injury in myelosis is, of course, caused or, at any rate, evidenced by the excessive productive activity of the lining histiocytes, which are not only vascular boundaries, but also hæmatopoietic tissues.

Some cases of myelosis fail to show an excess of leucocytes in the circulation, and it is difficult to understand the genesis of these aleukæmic cases on the theory propounded above. It is possible, of course, that even in the aleukæmic cases or aleukæmic phases of otherwise leukæmic cases of myelosis there is a great excess of myelopoiesis, which is more than counter-balanced by destruction of the emigrated cells. Szilard has noticed that the leucocytes obtained from aleukæmic cases are less resistant to the action of their own serum or to that from cases of leukæmic myelosis than are those of a leukæmic case. This writer concludes that the aleukæmic character of some cases of myelosis is due to excessive destruction of the less resistant leucocytes present in the blood. This suggestion does not, however, meet all the facts, because certain proliferative conditions of the hæmatopoietic organs occur in the total absence of any changes in the blood, *e.g.*, myelomata (p. 60), and without any evidence of excessive destruction of leucocytes in the body as a whole. We can do no more than suppose that the mechanism governing emigration of cells from the marrow varies at different times in the same case and in different cases of myelosis.

The appearance of immature leucocytes in the circulation in myelosis has often been attributed to a persistent demand for leucocytes; the continual drain has been supposed to

exhaust, completely or partially, the power of the marrow to produce an adequate number of mature leucocytes. Therefore, less differentiated forms have emigrated into the blood stream. Biological action and reaction, although opposite, are not necessarily or indeed usually equal, and so excessive numbers of immature cells appear. There are insuperable objections to this idea. It is known that, in the normal marrow, there is a stock of mature leucocytes, which seems to be very readily mobilisable to meet various emergencies. It is from this stock of cells that the leucocytosis occurring almost immediately after the onset of an infection is derived. In other words, the hæmatopoietic organs can, almost at a moment's notice, inject into the circulation a number of cells much greater than normal. If the demand persists, there will be appearance of less differentiated forms, viz., metamyelocytes, in the blood; and, in severe cases, even myelocytes may occur, but usually only in very small numbers. The question that arises in the discussion of myelosis is whether there is a deficient stock of mature leucocytes in the marrow because, if this is not the case, the view that the less differentiated elements appear because there are not enough mature cells is obviously inaccurate. I (2) have been able to show that, even in an advanced case of chronic leukæmic myelosis, there is far from being a deficit of mature neutrophiles; there is, in fact, a number much greater than normal. This was shown by performing leucocyte counts at hourly intervals for a period of twenty-four hours, during which the patient was kept in bed and was given ordinary meals. It was found that a digestive leucocytosis occurred to a degree far in excess of normal; and the type of cell, which was increased, was the neutrophilic polymorphonuclear leucocyte.

Another objection to the above conception is that it implies that the increased number of leucocytes in the circulation is the result of an increased demand for these cells in the blood, but there is no evidence of this; it is much more

probable that the excess of cells is due to the increased size of the myeloid tissue. If there were some peripheral stimulus, it would not be possible for aleukæmic cases to occur except at the end of life when the marrow was becoming aplastic; this is, however, not the case, because an aleukæmic stage may occur at any time in the disease, and may be either intermittent or persistent.

It can scarcely be emphasised too much that the number of circulating leucocytes is not a feature of vital importance in the diagnosis of any of the leucoses; particularly in myelosis it is the quality of the leucocytosis that is of significance. In different cases of myelosis the blood picture will be found to present wide variations, and this is even the case in one and the same individual, but, in all of them, the picture is characterised by the presence of immature cells of the myeloid series. As is described later (p. 100), there are cases of infection in which a "leukæmoid" blood picture occurs, and, in such cases, every kind of evidence must be taken into account in making a diagnosis.

The great majority of cases of chronic myelosis are characterised by increase of neutrophilic granular leucocytes, both in the blood and the formative tissues, but there is very often an associated increase of eosinophiles and basophiles, although of much less intensity. Cases in which some other form of granulocyte predominates are rare. Tomaschewski described a case in which over 35 per cent. of the leucocytes had basophilic granules, and Joachim recorded the occurrence of more than 80 per cent. Cases with predominance of eosinophiles are found mainly in French literature.

The blood picture of chronic myelosis, as seen at the first examination, can never be regarded as a stable condition; it will be found that, as the disease progresses, there will be striking changes. Even if at first there are no non-granular myeloblasts, these cells will, in almost every case, be found to increase gradually; the increase may occur in a few

weeks, in months, or may even take years to develop, but it practically never fails to appear. Briefly, the greater the percentage of myeloblasts in the blood the nearer is the patient to his end. Apart from the occurrence of intervening infection, the great majority of sufferers from chronic myelosis die at a time when the predominating cell in the blood is the myeloblast ; and, indeed, in their last stages they present the signs to be described shortly as being characteristic of acute leucosis ; this is true in the hæmatological sense and usually in the clinical one also.

Occasionally the predominating cell in the terminal stages is the premyelocyte (Alder), or even the myelocyte, but the fact that there has not been complete reversion to the most immature form of cell does not, in any way, affect the acuteness of the clinical manifestations. Cases in which the predominating cell is not the myeloblast are quite rare, and can scarcely be taken into account in estimating the acuteness of any given case, because we do not know which will be the ones that will never pass into the myeloblastic stage.

It is perhaps interesting at this point to refer to the great *splenomegaly*, which may reach so enormous a degree in chronic myelosis. Myeloid metaplasia is usually very extreme in the splenic pulp in chronic myelosis ; the Malpighian bodies become correspondingly diminished in size, and the organ takes on a histological appearance very similar to that seen in the embryo. The histiocytes lining the pulp spaces are also increased in number, and it is probably from them that the myeloid cells formed in the organ are derived. These histiocytes have, however, another important function ; they are found to be filled with remnants of degenerate leucocytes, and there can be little doubt that they function, even more actively than normal, as scavengers of the circulation. It seems probable that their great activity is the result, not only of being presented with a larger number of degenerate leucocytes for destruction than normal, but also

of many ill-formed cells reaching them in the circulation. The splenomegaly is thus the result of two hyperplastic processes; the one is adapted to increase the number of circulating leucocytes, and the other to reduce it.

Chronic Lymphadenosis may also occur in either a leukæmic or an aleukæmic form, but, in either case, is characterised by great overgrowth of lymphatic tissue; it is, nevertheless, rare for all the lymphadenoid tissue of the body to be equally involved in the process, and it is not uncommon for some of it to escape entirely; this fact makes it inconceivable that lymphadenosis is a system-disease of lymphatic tissue, as is contended by Naegeli.

There seems to be no particular reason for affection of one area of lymphatic tissue rather than another, but glands in some part of the body are always involved, and often the skin is the seat of nodular infiltrations; more rarely it is affected by a diffuse lymphatic hyperplasia, which gives rise to a clinical picture not unlike that of exfoliative dermatitis (Piney (3)).

The blood-picture is characterised by the presence of a great excess of lymphocytes, which are, in the chronic cases, almost all of the small type, although a few large forms, and even an isolated lymphoblast, can usually be found. An increase in the number of large lymphocytes and of lymphoblasts occurs as the disease progresses, and is of evil significance as being indicative of an acute termination; in short, exactly similar criteria of the degree of acuteness of the malady apply in lymphadenosis as in myelosis.

In the early stages there is little or no anæmia, but this invariably develops at some period; it may show a high colour index owing to the presence in the blood of macro-normocytes, *i.e.*, the non-nucleated offspring of the partially hæmoglobiniferous macro-normoblast. Although these large corpuscles are not fully hæmoglobiniferous, their great size permits them to carry a considerable amount of pigment, and this accounts for the slight rise of colour index. At

about the time of first appearance of nucleated red cells in the circulation, immature myeloid leucocytes in small numbers also appear. These " myeloid " appearances occur ultimately in all cases of lymphadenosis that live sufficiently long, whether they be leukæmic or aleukæmic in type; further, the myeloid changes tend to become more marked in the later stages of the disease, even if leukæmic and aleukæmic phases occur during its development.

A variable number of the circulating lymphocytes in this malady show excessive basophilia of the cytoplasm, which, in these circumstances, always becomes more bulky than normal. Such cells were described by Türk as " Reizungsformen," and may, in very rare cases of lymphadenosis, form the majority of the lymphocytes in the blood. There is no doubt that these cells, as seen in lymphadenosis, are modified lymphocytes, but it must be realised that such excessive cytoplasmic basophilia may occur in any non-granular blood cell, although it is rare, except in lymphocytes and lymphoblasts. In association with such protoplasmic change in the lymphocyte it is usual to see nuclear alterations, which tend in the direction of a greater distinctness of the basi- from the oxy-chromatin, together with a tendency to a radial arrangement. The development of such a " cart wheel " type of nucleus is often associated with further increase in the amount of cytoplasm; as the protoplasm becomes relatively bulky the nucleus tends to take up an excentric position and be surrounded by a pale area. Minute vacuoles occur in the cytoplasm, and so arises a cell with the characters of a plasma cell. Such lymphocytic plasma cells are often present in the blood in very small numbers in cases of lymphadenosis, but as a rarity may form the majority of the circulating cells in the blood and hæmatopoietic organs. I have recorded one such case in which the number of plasma cells in the circulation exceeded 40 per cent. Other non-granular blood cells may undergo a plasmocytoid change, and so there can arise erythroblastic,

myeloblastic, lymphoblastic and monocytic plasma cells, but these are all rarities, and are, of course, not seen in lymphadenosis of ordinary type.

The tendency for the number of immature cells to increase, both in cases of myelosis and of lymphadenosis, has already been mentioned, and, in the advanced stages of these maladies, there may be definite resemblances between the two blood pictures. This has led some observers to record cases of "change of type" of leukæmia and also "mixed" leukæmias. There can be no doubt that, in such circumstances, the writers have failed to discriminate between the myeloblast and the lymphoblast. The adherents of the monophyletic school do not regard these cases as being "mixed" in type; they are of opinion that the non-granular cell appearing in the blood is the common ancestor (lymphoidocyte or hæmocytoblast), and, therefore, they speak of lymphoidocytic, hæmocytoblastic or stem-cell leukæmias. An example of such an interpretation has been described by Gordon and Chesney. They record a case in which there were many small non-granular cells in the blood; these were clearly immature elements, inasmuch as they contained nucleoli. They term these cells "microlymphoidocytes," as Fineman had done in a previous case. Now the whole conception of the lymphoidocyte is a purely theoretical one, and the "microlymphoidocyte" is presumably a cell-type invented to meet the exigencies of the occasion. Small forms of myeloblasts and of lymphoblasts are known to occur in embryonic life, whereas the lymphoidocyte is only a conception born of convenience in explanation. In Gordon and Chesney's case there were, at one time, over 2,000 myeloid leucocytes per cubic millimetre in the circulation, and over 500 erythroblasts per cubic millimetre. In view of this well-marked "myeloid" admixture to the blood picture, it would be well to inquire whether this case was not a lymphadenosis (as was shown to be the case in their careful histological report) in which there were many very

immature myelocytes in the circulation as a result of marrow stimulation of the kind to be discussed later (pp. 130 *et seq.*). It is my impression that all reports of change of type of a leukæmia or of stem-cell leukæmias can be traced either to failure to distinguish the myeloblast from the lymphoblast, or to the presence of excessive myeloid reaction in a case of lymphadenosis. In the same way some cases of secondary neoplasia of the bone marrow have been regarded as being true leucoses until autopsy revealed their real nature, *i.e.*, an extreme myeloid reaction (leukæmoid reaction) obscured the primary malady.

It has often been claimed that the myeloblast can be distinguished from the lymphatic stem-cell by the demonstration of enzymes in the former. Schultze introduced the " oxydase reaction," which was stated to be positive only in cells of the myeloid series, and so to be a differential feature between any of them and the lymphatic cells. Dunn showed that some cells, which were morphologically myeloblasts, gave no oxydase reaction. I (5) have shown that the oxydase reaction occurs solely in cells of the myeloid series, but only if they contain granules, which may, however, be so fine as to require very careful staining methods (Appendix I.). In other words, the oxydase reaction is positive only from the stage of the earliest premyelocyte onwards. It is essential to realise that the first formed granules of the premyelocyte do not have the same staining reaction as do those of the fully developed cell ; they are definitely azurophilic in their earliest states, but, even so, the cells can be arranged into groups (Ferrata) :—

Premyelocytes with the nuclear characters of the myeloblast, but with azurophilic granules, may occur in the following forms : with minute, evenly distributed granules, the preneutrophilic premyelocyte ; with large, evenly distributed granules, the pre-eosinophilic premyelocyte ; with large granules irregular in size and distribution, the prebasophilic premyelocyte.

All these forms give a positive oxydase reaction, but the recognition of the completely non-granular myeloblast and its differentiation from the equally non-granular lymphoblast must be made on purely morphological grounds.

There is another form of leucosis, which, although rare, is of great theoretical importance. Clinically, its course is intermediate in length between the chronic and the acute cases. There is much objective evidence of severe involvement of both functions of the bone marrow, viz., leucopoiesis and erythropoiesis. The blood, which may be leukæmic or aleukæmic, contains immature leucocytes in large numbers, and, in addition, there are very many erythroblasts of normoblastic type in various stages of development. Anæmia is severe and progressive, but the erythroblasts in the circulation appear to vary in number quite independently of the intensity of the anæmia. The colour index is commonly above unity, and this has led some observers to regard this disease as a sort of mixture of leucosis and pernicious anæmia (leukanæmia of Leube (p. 93)). It is more usual to presume that the malady is a pure myelosis in which all the functions of the marrow are involved (panmyelosis). If this idea be accepted, we have again evidence of the view held in this book that red cells and granulocytes have a common ancestor, which gives rise to two sorts of offspring in different environments, viz., intra- and extra-vascularly respectively. The term erythroleukæmia has been proposed for this form of general involvement of the marrow (Ferrata), and seems to meet the requirements of the case. It must throughout be realised that we are dealing with a proliferative process of the parent reticulo-endothelium, which is performing both its functions in an excessive manner; it is not, however, producing lymphocytes also, because the marrow is not a suitable environment for the process of lymphocytopoiesis.

A brief account of the **Acute Leucoses** is now convenient; these, like the chronic forms, can be divided into lymphatic

and myeloid cases, although there are no noteworthy clinical differences. Only the primarily acute cases are to be discussed here, but clinically it must always be borne in mind that most chronic cases of both myelosis and lymphadenosis end in an acute manner.

Acute Myelosis is usually leukæmic or sub-leukæmic; true aleukæmic cases are very rare. The vast majority of the cases show a very high percentage of myeloblasts in the blood and formative tissues, but rarely the predominating cell may be the premyelocyte (Alder).

Cases of acute leucosis in which the predominating cell-type in the circulation is the monocyte (large hyaline leucocyte) are rare, but present points of extreme interest.

The classification of these cases has presented, and, indeed, still presents, considerable difficulties, because such writers as Naegeli include these with the myeloses, while others will not do so. Naegeli bases his contention on the presence in the blood of transitional forms between monocytes and myeloblasts, on the frequent termination of the cases as acute myeloblastic leukæmia, on the positive oxydase reaction of the circulating monocytes, and on the characters of the histological changes in the organs. As is well known, Schilling takes the view that monocytes are derivatives of the reticulo-endothelial system, and supported this idea in the first recorded case of *monocytic leukæmia* (Reschad and Schilling). He states that the cells may be oxydase-negative, or at most very slightly positive, and contends also that there is evidence of very little involvement of the granulocytic system, which is surprising if Naegeli's view is correct. The last contention is scarcely supported by the observations of Hittmair, who found that there was a prodromal anæmia of severe degree in his cases; this must be regarded as being the direct result of implication of the granulocytic system in the pathological process.

Hoff records a case in which the monocytes rose to over 40 per cent. of the total leucocytes, and states that many

of them had the characters of endothelial cells, *i.e.*, possessed a sort of tail. The case was striking also because the number of leucocytes never rose above 2,500 per cubic millimetre. We have already emphasised the great importance of the reticulo-endothelium in the whole process of hæmatopoiesis, and could, therefore, scarcely be surprised if cases of leucosis occurred in which dislocated reticulo-endothelial cells appeared in the circulation. Ferrata states that such cells (hæmo-histioblasts) occur in many cases of myelosis and lymphadenosis. Further, we have to realise that it may often be very difficult, or even impossible, to distinguish a young monocyte from a myeloblast; so much is this the case that Ziegler contended that monocytes were nothing more than slightly differentiated myeloblasts.

The really essential point is that, if we are prepared to admit, with Ferrata, that dislocated reticulo-endothelial cells (hæmohistioblasts) can and do occur in the blood in any form of leucosis, we cannot use this fact as a support for the conception that monocytes are special derivatives of this system. The evidence seems to be all in favour of the conception of monocytic leukæmia belonging to the group of myelosis, and not being a special form of leucosis depending upon proliferation of the cells of a third hæmatopoietic system.

Acute Lymphadenosis is accompanied by changes in the blood, which, at first glance, seem to resemble those of acute myelosis, but the morphology of the large non-granular cells, which form the majority of the circulating leucocytes, is that of the lymphoblast. The histological changes in the body are also fundamentally different in the two diseases.

Our knowledge of the process of *formation of blood platelets* in the leucoses is woefully incomplete. In lymphadenosis there is always progressive diminution of platelets, which rather supports the idea of their origin from some constituent of the marrow, which is being injured and destroyed by the growth of lymphatic tissue.

Minot and Buckman state that, in chronic myelosis, the number of platelets is rarely much increased or much decreased. A shift of the number of platelets towards normal at the same time as an improvement in the condition of the leucocytes forms additional evidence of effective treatment, but alteration in the number of platelets alone is not of significance. The petechial hæmorrhages, which occur in both forms of leucosis, but most frequently in lymphadenosis, occur at times when the number of platelets is low, but, of course, other hæmorrhages may occur as a result of ulceration of leukæmic masses on a free surface, even when the platelet count is normal or raised. It is interesting in this connection to note that Minot has found megakaryocytes in the circulation in cases of chronic myelosis, and attributes the dyspnœa, which is so well marked in some cases, in part at least, to the presence of these cells as emboli in the lungs. Körner described a great proliferation of megakaryocytes in the tissues in a case of acute myeloblastic leukæmia under his observation, but does not mention their presence in the blood; they were probably not numerous in the circulation because comparatively few were found in the lungs, which could scarcely have been the case if they had been available as emboli. Their occurrence in the tissues, in this case, must be regarded as indicative of myeloid metaplasia of a special type.

The *histogenetic problems* of the leukæmias can obviously find their solution only in the formative organs, and not in the blood. Before discussing the nature of the histological changes, it will be well to refer to the observations of Lenaz on certain allied subjects. This writer contends that the determination of the nature of a proliferative process must be preceded by a definition of the terms to be employed. He defines *hyperplasia* as an increase in number of normal cells in normal arrangement; increase of apparently normal cells, in abnormal distribution, is not an identical process. The histological criterion of inflammation and organisation

of inflammatory tissue is based upon observation of progressive differentiation of immature cells, so that there ultimately come to be cells of many types in the tissue. Such a condition is very different from that seen in the case of a malignant tumour, *e.g.*, a sarcoma, where there is proliferation of only one type of cell, which shows very little tendency to differentiate, and certainly shows no sign of its conversion into a more complex cellular element, *i.e.*, in a tumour, there is only one type of cell, and that is of embryonic character. Lenaz, therefore, states that the essential feature of neoplasia is the presence of a *mono-phasic anaplasia* (reversion of one cell-form to embryonic type). Inflammatory and organising lesions are characterised by a *polyphasic anaplasia*, and so show very different histological appearances. We must bear these definitions in mind throughout the discussion of the anatomical changes in the leucoses.

In myelosis the histological changes occurring outside the bone marrow itself are essentially those of myeloid metaplasia, *i.e.*, formation of marrow tissue outside the medullary cavities of bones. Ziegler imagined that the growth of such cells in foreign tissues was the result of settling out of cells from the circulating blood, but it has already been shown (Chapter II.) that blood cells can be formed wherever reticulo-endothelial tissue is available ; the hypothesis of colonisation from the blood stream is, therefore, unnecessary.

In lymphadenosis, the whole of the lymphatic tissue of the body shows great overgrowth with loss of the normal arrangement, *i.e.*, into follicles ; it is, thus, not a simple hyperplasia in the sense of Lenaz's definition. It is naturally difficult to make out details of the histogenesis of the process in places where so many cells of the same type are present, but when lymphatic cells develop in a different tissue, the problem is easier ; in all cases of lymphadenosis there is, at some stage, invasion of the bone marrow by lymphocytes, and here the distribution of the cells is most easily followed (see later).

The arrangement of the infiltrations in the various organs differs very considerably in myelosis and lymphadenosis respectively. The spleen, in myelosis, shows well-marked myeloid metaplasia of the pulp with consequent diminution in size of the Malpighian bodies, whereas in lymphadenosis the Malpighian bodies become large at the expense of the pulp. Probably no better demonstration of the bi-partite structure and function of this organ could be obtained.

The liver, in myelosis, is the seat of myeloid metaplasia around the intra-lobular capillaries, and to a less extent in the portal tracts ; in lymphadenosis, the infiltration with lymphocytes is confined to the peri-portal connective tissue (peri-portal lymphomata) (Naegeli).

The marrow in myelosis shows most complex changes ; the cases which die in an acute myeloblastic stage always show much overgrowth of the reticulo-endothelial tissue, which is, of course, composed of the hæmohistioblasts of Ferrata (p. 19). This writer states that such hæmohistioblasts may appear in the circulation in considerable numbers in myelosis, particularly in the acute form. Ferrata and Reitano describe this condition of hæmohistioblastic leukæmia, but do not seem to adduce good evidence that all the very immature cells illustrated are really dislocated reticulo-endothelium. As would be expected, they describe hæmohistioblasts also in cases of lymphadenosis. Here we shall probably be safer to regard the proliferation of reticulo-endothelium as evidence of increased formative activity rather than as being a direct contributor of its own unaltered cells to the number of circulating leucocytes.

The marrow in a case of myelosis shows, as might be expected, an enormous richness of cellular content, particularly of leucocytes. The earlier the case the greater will be the relative number of the more mature forms, whereas in the later stages the myeloblast will dominate the picture. The most striking feature of the histological picture, even in fairly early cases, is the presence of small masses of cells

composed entirely of one type of element. The individual constituents of these masses show no signs of any attempt at further differentiation, although they are surrounded by actively proliferating and differentiating cells. Usually these cell clusters, in which there may be several hundred cells, are composed of myeloblasts; much more rarely they are purely premyelocytic or even myelocytic. My own contention (6) is that the type of cell that predominates in the blood in the terminal acute stages of chronic myelosis will always be found to be of the same type as that composing the intra-medullary masses. This would be in conformity with the known frequency of the myeloblastic, premyelocytic and myelocytic forms of acute leukæmia. These masses, composed entirely of one type of cell (Fig. 5), lie in the midst of hyperplastic marrow tissue; it is from an investigation of the reciprocal effects of these two possible sources of cell-formation that we can expect explanation of the changes in the circulating blood. We might suppose that the blood picture is composed of contributions both from the focal aggregations and from the hyperplastic marrow tissue; it is fortunate that there occurs a pathological condition supporting this view.

It is not uncommon for metastases of malignant tumours to be found in the medullary cavities of bones. They reach this centre of hæmatopoietic activity by way of the blood stream, and are found in an intra-vascular position in the marrow. It is commonly held that there are no lymphatic channels in bone marrow, and that, therefore, the hæmic route is the only one available. Recently Kolodny has criticised my statement that the myeloid tissue is free from lymphatics, although he has been equally unable to demonstrate their existence directly. He relies upon the results of intra-medullary injections of particulate material, which he states is transferred from the marrow into lymphatic glands; he concludes that no explanation other than the existence of lymphatic channels would explain this occur-

rence. A lymphatic which cannot be seen is scarcely a satisfactory morphological entity, quite apart from the fact that

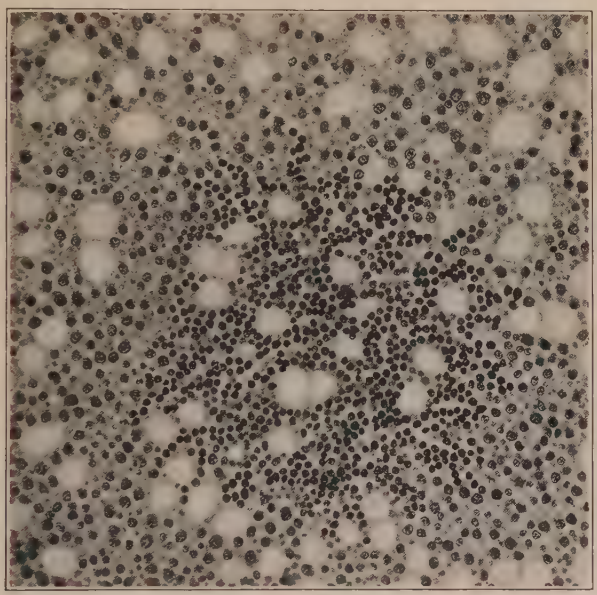


FIG. 5. The picture shows a portion of the femoral marrow of a case of chronic leukæmic lymphadenosis, which showed the characteristic blood picture of an advanced case of that disease, and 2·15 per cent. of immature myeloid cells were present.

In the middle of the picture there is a small collection of cells which are all of the same type, and are definitely smaller than any of the cells of normal bone marrow; they all had the characters of small lymphocytes. The cells surrounding the focal collection of lymphocytes are of the varieties seen in normal myeloid tissue, but their number is very considerably in excess of that found in normal adult marrow, and the quantity of fat is distinctly reduced. Comparison with Plate IV. will show that the presence in the marrow of other abnormal cells is also accompanied by hyperplasia of the myeloid tissue proper, and, therefore, it is justifiable to suppose that the hyperplasia in the present case is the direct result of stimulation of the marrow by the collection and growth of masses of lymphocytes.

The mass of lymphocytes seems to be composed of cells which are all of the same type, and, as they are cells of a character normally absent from the marrow, it is difficult to escape the conclusion that they are truly neoplastic masses. (Reprinted from "The Neoplastic Nature of the Leukæmic Process." A. Piney. *The American Journal of the Medical Sciences*, 1925, vol. clix., p. 691.)

it is difficult to understand any possible function of such passages in a tissue the constituents of which are continually emigrating, although never leaving by a lymphatic route. The absence of lymphocytes from the normal marrow seems completely to negative the idea of the existence of lymphatic channels in the marrow. In any case, metastases of malignant tumours, whether sarcomatous or carcinomatous, can be found lying inside blood vascular channels (Plate IV., Fig. 37). One would expect that there would be far-reaching effects on erythropoiesis, which has already been described as an intra-vascular process; this is indeed the case, as is shown by the appearance, in the circulation, of large numbers of macro-normoblasts and normoblasts (Piney (6), (7), (8)). There is as a rule also some degree of anæmia which may show a high hæmoglobin index, and in so far simulate pernicious anæmia (Harrington and Teacher). There is also an invariable alteration in the composition of the leucocytic blood picture; this is often quantitative, but is always qualitative. There may be great leucocytosis, but the number of leucocytes may be normal or even decreased; there is invariably appearance of immature leucocytes of the granular series in the circulation, and this is the really important change. Even the myeloblast may appear, but, as a rule, myelocytes are much more numerous. The effect on the circulating blood is thus the production of a picture closely resembling erythro-leukæmia, *i.e.*, anæmia, many nucleated red cells and immature leucocytes; to such blood pictures the term "leukæmoid" reaction can well be applied. If such a case be followed to its termination it will be noted that the percentage of the most immature cells does not necessarily or even usually increase towards death. The absence of an acute myeloblastic termination in these cases suggests that the immature leucocytes in the circulation are derived from a marrow which is truly hyperplastic but in which no deviation from the normal type of hæmatopoiesis has occurred. In very prolonged cases, the leukæmoid blood

picture may disappear and be replaced by one suggesting the occurrence of aplasia of the marrow; this occurs as the result of widespread destruction of myeloid tissue by tumour cells, but is never accompanied by anything resembling acute myeloblastic leukæmia. It seems clear that there is more than a purely mechanical extrusion of cells from the marrow into the circulation. Such an explanation might suffice for the erythroblasts, which are intra-vascular formations, but the leucocytes, which are extra-vascular, would be affected only if the mass of neoplastic cells acted as an irritant to which the leucopoietic mechanism responded by proliferation and emigration through the damaged vessel wall (see also Chapter VI.).

There seems to be no good reason for supposing that the foci of cells embedded in the myeloid tissue in cases of leucosis would have an effect in any way different from that due to the presence of metastatic tumours; they would irritate the surrounding hæmatopoietic tissue to excessive proliferation in a similar manner, and might be expected to cause a similar blood-picture. The character of the blood in the leucoses is not, however, identical with that associated with metastatic cancer of the marrow; this must be attributed to the fact that the irritating masses of cells are themselves potential blood cells. The present contention is that the blood picture of the leucoses is a composite one in which cells derived from the simple hyperplasia of the marrow reach the circulation together with other elements coming from the focal aggregations of atypical blood cells.

It has already been mentioned that when a metastatic cancer of the marrow becomes extensive, an aplastic condition of the myeloid tissue develops and shows itself in the blood by decrease or even practical disappearance of leucocytes, and great reduction of red corpuscles. When leucotic foci become very large they also destroy the myeloid tissue which they previously stimulated to greater endeavours, but the blood does not show the same signs of

aplasia as are seen in the metastatic cases; this depends upon the fact that cells continue to emigrate from the focal masses which are composed entirely of one type of cell. This must be the explanation of the monotonous character of the blood picture in the last stages of a secondarily acute myelosis in which practically all the normal granulocytopoietic cells have been destroyed. Further, it is clear that the focal masses, although composed of cells with many of the characters of myeloid or lymphatic cells respectively, differ in their resistance, *i.e.*, these focal aggregations are structures independent of the ordinary myeloid tissue.

The conditions in lymphadenosis are more easily detected because masses of lymphocytes in the midst of the marrow are extremely easily recognised; the changes in the neighbouring marrow tissue are identical in quality, although much less in intensity, with those of myelosis. It is this hyperplasia which accounts for the appearance of myeloid cells in the blood in lymphadenosis. The observation of Naegeli that spontaneous fracture can occur in chronic lymphadenosis further increases the resemblance of this process to metastatic tumours of bones.

Ellermann has shown that the angle formed by the spindle in the process of karyokinesis is always the same in the same type of cell; this method of investigation supports the view that all the cells composing the leucotic masses in the marrow are of the same type.

The nature of the leukæmic process is still a matter of dispute; in the last section of this chapter there is a description and discussion of the infective leucosis of fowls, but I can feel no certainty that this disease is identical with human leucosis.

Sternberg has been an ardent supporter of the view that some cases of leucosis are truly neoplastic in character, but he has regarded the acute forms as representing a special type of reaction to various infections, and, therefore, as maladies essentially different from the true leucoses. He

admits that the acute termination of the chronic cases is a true leucosis; but regards the primarily acute forms as being "leukæmoid" reactions, such as are discussed in Chapter V.

The observations of Lenaz on the essential criteria of neoplasia make it clear that the proliferation of the marrow cells around the leucotic foci cannot be regarded as being of the character of tumour formation. The foci composed entirely of one type of cell do, however, correspond to his conception of a mono-phasic anaplasia, and must, therefore, be regarded as being neoplasms. It has often been objected to the neoplastic hypothesis of leucosis that many cases of the disease have a very long clinical history, but it is not necessary to suppose that all leucotic tumours are malignant or, at any rate, highly malignant. Exactly similar arguments apply to lymphatic leucosis where the two conditions of hyperplasia and neoplasia are less easily distinguished, except in the marrow, where the two processes are very distinct. It is known that neoplasms composed entirely of immature blood cells may occur (myelomata); these would, on the present hypothesis, represent the most innocent and, therefore, least irritating forms of leucosis.

The present contention is, thus, that leucosis in all its forms is neoplastic in nature; the blood picture of the disease is composed of cells emigrated from the foci of tumour cells together with other immature cells derived from the hyperplastic hæmatopoietic tissue around the tumours.

The **Treatment of the Leucoses** is as unsatisfactory as is that of all neoplasms, with the additional disadvantage that the leucotic tumours are not surgically accessible. The use of X-rays in suitable doses is attended with a very partial success. The dangers of this mode of treatment are discussed in the section on Aplastic Anæmia (p. 164). It is possible with this mode of treatment to reduce the number of the circulating leucocytes and to cause a more normal composition of the leucocytic blood picture in the leukæmic

cases, while in the aleukæmic forms of the malady less benefit is obtained, and the risk of inducing aplasia is greater. Continual examination of the blood to detect the earliest signs of progressive anæmia and of increase of immature leucocytes is essential. It has been shown (Minot and Isaacs, Piney (9)), that the expectation of life in treated cases of myelosis is not improved, but the period of efficiency is much greater than in patients left untreated or given only medicinal treatment.

It is important to realise that the number of circulating leucocytes can be reduced by other measures; benzol, administered in capsules, has had much popularity. Like X-rays, benzol is capable of causing aplasia of the bone marrow, and can, therefore, in suitable dosage, cause a slower rate of blood formation. There can be no doubt that administration of benzol in cases of leukæmic myelosis is attended by a marked improvement in the blood picture, but the clinical state of the patient may remain unchanged, may become worse, or may improve quite independently of the hæmatological findings.

Benzol is not known to exert any effect upon the growth of neoplasms, whereas X-rays do so quite commonly. The explanation here advanced of the different therapeutic effects of benzol and X-rays respectively in leukæmic myelosis is that the former injures and reduces the activity of the hyperplastic marrow around the leukæmic foci, whereas X-rays have a less powerful effect upon it, while damaging the neoplastic cells. If the dosage of X-rays be too great, aplasia of the whole marrow will occur, but that does not affect the present argument.

It is not difficult to show that the effect of X-rays upon lymphatic leucotic tissue is less intense than upon myeloid cells; in conformity with this there is, as would be expected, much less good to be obtained from irradiation in cases of lymphadenosis, which in any case tend to have a longer expectation of life even without treatment.

Chloroma and Myeloma

Chloroma used to be described as a special form of neoplasm (cancer vert of Aran), characterised by a green colour immediately on removal from the body. The characteristic site of the tumours is the periosteum of the skull bones, particularly of the orbit. Von Recklinghausen found that the disease was always associated with the occurrence of histological changes identical with those seen in cases of leukæmia.

The great difference between those cases of leucosis which run the typical course, and those termed chloroma lies in the formation, in the latter condition, of definitely infiltrating nodules. It is not possible to regard chloroma as a special form of sarcoma of hæmatopoietic tissue because of the associated leukæmic blood picture, but, of course, if the present contention that all leucoses are sarcomatous be admitted, no difficulty arises. It is well known that infiltrative growths with the characters of a large-celled lymphosarcoma may be associated with a lymphæmic blood picture (leucosarcomatosis of Sternberg). The changes in the organs are those of leucosis, but one or more of the masses becomes large and infiltrative. Chloroma appears to differ in the presence of the peculiar green colour, and in that the blood picture is always myeloid in type.

Those tumour-like cases of leucosis in which green coloration is present appear all to be of myeloid type, and invariably run an acute course, although the patient may in rare cases live for six months.

Naegeli contends that chloro-leukæmia is a system disease of hæmatopoietic tissue, and, therefore, cannot be sarcomatous. It must be emphasised that not all the blood-forming tissue in the body is equally affected, and indeed some may escape completely; the conception of a system disease is clearly untenable. He is prepared to admit that there is no good reason for separating the chloro-leukæmias from the other

forms, and thus admits that an explanation of the nature of the one process would apply equally to the other.

To pursue personal opinions further is tempting in view of the fact that chronic leukæmias, acute leukæmias and infiltrative leukæmias have already been described; in each case there has been an associated leukæmic or sub-leukæmic change in the blood picture. If now it is possible to demonstrate the occurrence of tumours composed of hæmatopoietic cells, but not associated with alterations in the circulating blood, we shall have a complete series of such growths extending at the one end from a completely innocent (and, therefore, practically non-irritative) tumour to frankly malignant growths at the other, while the chronic leucoses appear as intermediate types of a less degree of malignancy than the more obviously sarcomatous ones.

The innocent member of this series of tumours of hæmatopoietic tissue is the **Myeloma.**

A few words to make clear the nomenclature of these growths are an essential preliminary, because, unfortunately, the name "myeloma" has been applied to a variety of unrelated new formations of tissue.

It is clear that the term "myeloma" can be properly applied only to tumours composed of cells of the type normally found in the bone marrow, viz., they can be myelocytomas, myeloblastomas, erythroblastomas; rarely, lymphocytomas or lymphoblastomas or even plasmocytomas.

It is quite unjustifiable to refer to the giant-celled tumour of bone (myeloid sarcoma of older writers, osteoclastoma of M. J. Stewart) as a myeloma, because the giant cells, in this case, are not megakaryocytes, and there is no evidence at all that these growths take their origin from any constituent of the marrow. Equally the term must not be applied to the giant-celled tumours of tendon sheaths, where foreign-body giant cells and many lipoid-containing cells are present; even the rather popular name "xantho-myeloma," is not satisfactory, because it suggests some relationship to marrow.

The formation of tumour-like nodules in many bones is not alone evidence of the malignancy of the myelomatous process, and equally the destruction of bone tissue can be explained as the result of pressure rather than as due to malignant infiltration.

One of the features of importance in the diagnosis of multiple myelomatosis (Kahler's disease) is usually held to be the occurrence of Bence Jones protein in the urine. Hirschfeld was able to show that, in a series of 78 cases, it was absent in 42 ; its occurrence is, therefore, not invariable. Further, Decastello and Askanazy have observed the occurrence of this substance in the urine in lymphatic leukæmia ; Zuelzer found it in the urine of dogs poisoned with pyrodin ; rarely, even secondary deposits of malignant tumours may be associated with Bence Jones proteinuria.

The fact that Bence Jones protein may occur in the urine in cases of lymphatic leukæmia suggests that it cannot possibly arise either from the foci of lymphocytes in cases of lymphadenosis or from the myelomatous masses in Kahler's disease ; it must clearly be derived from some special mode of breakdown of the marrow tissue. This appears to be a clear demonstration of the essential difference in nature between the myelomas and the marrow tissue, although they are both composed of hæmic cells ; if the difference were so slight as to be negligible, one would not expect to find evidence of any deleterious effect of the myelomas on marrow function.

Myelomas do not necessarily affect a number of bones ; they may be isolated masses occurring in a single skeletal structure ; and in either type of case may be of the nature of myeloblastoma, myelocytoma, lymphocytoma, lymphoblastoma, plasmocytoma or erythroblastoma.

There seems to be no gap in the series of tumours described ; a continuous gradation between single myelomas on the one hand and generalised leucotic processes on the other has been discussed. It seems difficult to escape

from the view that the leucotic process is a truly neoplastic one.

The subject cannot properly be left at this stage because so much discussion of the nature of leucosis has hinged on the occurrence of spontaneous and experimentally induced leucosis in the fowl.

Ellermann states that the malady may affect fowls as a lymphatic leucosis, a "myeloic" leucosis, an intra-vascular lymphatic leucosis, or as a pure anæmia of "pernicious" type. The blood pictures in these conditions resemble those seen in the corresponding forms of leucosis in man, except in the case of the anæmic and the intra-vascular lymphoid type. The last-named variety is not associated with appreciable changes in the circulating blood, but there is enormous accumulation of non-granular mononuclear cells in the vessels of kidneys, liver, spleen and bone marrow; to this condition he refers as leucostasis. In the anæmic type there is leucostasis in the marrow only, and the other organs present little change, while the blood shows a severe anæmia.

Ellermann claims that the disease is sometimes transmissible from fowl to fowl by inoculation of cell-free filtrates, but McGowan has thrown much doubt on this idea, and is of opinion that the changes of leucosis in fowls can be brought about by a number of ætiological factors, such as tapeworm infestations and respiratory diseases. He has certainly shown that direct extension of irritation from the peritoneal cavity to the marrow can occur in birds.

The main resemblances between the leucosis of fowls and pernicious anæmia in man are clinical ones, such as lemon-yellow colour of the skin, a tendency to the occurrence of remissions and to adiposity. It appears to me that the whole question is one of revival of the old conception of leukanæmia; this has already been discussed and the conclusion reached that it is not, as a rule, a mixture of leucosis and pernicious anæmia, but is a pan-myelosis, *i.e.*, an erythro-leukæmia. This would form an adequate explanation of the case recorded

by Sebastiani, in which a "hæmocytoblastic" (? myeloblastic) leucosis passed through a more differentiated stage back to its original form. During one aleukæmic period he states that the blood showed all the characters of pernicious anæmia; it must be pointed out that his criteria of pernicious anæmia do not seem to be as well defined as those laid down in Chapter IV.

Apart from the blood picture, the only notable resemblance between leucosis as it occurs in the fowl and in man lies in the fact that osteo-sclerosis may occur in both, but is infinitely commoner in the fowl. The very fact that no leukæmic lymphadenosis is known in the fowl seems to suggest that the leucoses of this animal are entities quite separate from human leukæmia.

The importance and interest of the investigations of the peculiar leucotic disease of fowls cannot be denied, but the question of its relationship to human leukæmia is quite unsettled; and, for the present, it is well to regard them as being distinct diseases. Ellermann's monograph should be consulted for a detailed account of the avian disease.

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CHAPTER IV

PERNICIOUS ANÆMIA

It is convenient to present an account of pernicious anæmia at the present stage, because there have recently been many statements that it is a malady closely related to the leucoses.

The history of the growth of our knowledge of pernicious anæmia has been reviewed by many writers, particularly by William Hunter ; the present purpose can best be served by describing the individual manifestations of the disease separately, while taking for granted that the reader is not completely devoid of knowledge of the malady.

The most notable feature of this disease, as of all other forms of anæmia, is to be found in the hæmatopoietic tissues, and therefore in the circulating blood also.

The **Anæmia** is characterised by reduction both in the number of red corpuscles and the amount of hæmoglobin, but the latter is relatively less diminished than the former. In other words, the anæmia is associated with a colour index above unity, which, of course, implies that the average amount of hæmoglobin per corpuscle is increased. Such a condition can appear only if the average size of the corpuscles is abnormally great, because normally each corpuscle contains as much hæmoglobin as it will hold ; an increased content of pigment can, thus, occur only if larger corpuscles are available. Alder has been able to show by a viscosimetric method that the average volume of the corpuscles in pernicious anæmia is definitely greater than normal, and Price Jones has demonstrated, by a very laborious graphic method, that the average diameter is also abnormally

great; further, the mean variation in size is beyond normal limits.

Examination of stained films shows clearly that, in addition to much variation in size (anisocytosis) of the corpuscles, there is considerable variation in shape (poikilocytosis); the most striking feature, however, is the presence of a variable number of unusually large fully hæmoglobiniferous red corpuscles (megalocytes).

The *anisocytosis* is to be regarded as evidence of the occurrence of active regenerative processes in the bone marrow; and, therefore, as might well be expected, this appearance is entirely absent in conditions of aplasia of myeloid tissue. Although anisocytosis is a regeneratory phenomenon, it is, of course, not quite a normal accompaniment of restoration of the blood, and is scarcely present in health; it is, therefore, to be considered as being evidence of an excessively hurried regeneration.

Poikilocytosis is to be interpreted in a similar manner, but is a more definitely abnormal mode of regeneration than is anisocytosis, inasmuch as it is not seen at all in health, whereas, even normally, there is a slight variation in the size of red corpuscles.

Punctate basophilia is quite commonly seen in pernicious anæmia, particularly during recovery from a relapse. The absence of this appearance from the blood in cases of aplastic anæmia makes clear the regeneratory significance of the phenomenon, but its absence from embryonic blood corpuscles indicates that it is a sign of abnormal regeneration.

Polychromasia, in varying degree, is commonly encountered and indicates active regeneration of normal type; in fact, it can be stated that polychromasia is simply a condition of slight immaturity of red corpuscles, and so its presence in the blood implies nothing more than emigration of elements, which are almost, but not quite, ready for the circulation.

Nucleated red cells appear in the blood at some time in all cases of pernicious anæmia, but cannot be regarded as being pathognomonic of the disease. The greater the severity of the anæmia the larger the number of normoblasts in the circulation; these cells always tend to appear in the blood in response to the stimulus of insufficient oxidation, and their significance is, therefore, no greater than is the presence of the anæmia itself. Megaloblasts (Plate III.) also appear in the blood, and, at all times, seem to be in excess of the number of normoblasts. Their number is greatest during the definitely anæmic stages of the disease, but isolated specimens can often be found even during remissions. In a few very rare cases there occurs a so-called "blood-crisis" during a relapse; this is a condition in which large numbers of normoblasts appear in the circulation for a few days. Such a crisis is usually followed by transient improvement, but never ushers in a well-marked persistent remission. This is the only stage of pernicious anæmia in which normoblasts are ever found in greater numbers than megaloblasts; it must presumably represent an intense regeneratory effort on the part of the marrow, and it is very striking that, in so intense a reparatory process, the megaloblast appears to be of no importance; it is, in other words, an excessive regeneration, which is, nevertheless, normal in type.

The **Leucocytes** in pernicious anæmia present no very spectacular changes, but there are always noteworthy alterations.

Decrease in the number of leucocytes (leucopenia) is usual, but low normal figures are quite commonly encountered. The leucopenia depends almost entirely upon reduction in the number of neutrophiles; and this phenomenon is present even in those cases in which a normal number of leucocytes occurs. As a result of the neutropenia, there is relative lymphocytosis, which doubtless depends upon the absence of pathological changes in lymphatic tissue in this disease.

The characters of the neutrophiles present some interesting features ; immature cells (metamyelocytes and even myelocytes) may be present in small numbers during relapses, but in spite of this evidence of hurried emigration of neutrophilic cells, there is also some indication of hyper-maturity, inasmuch as it is always possible to find some neutrophiles which are much larger than normal and have an excessive number of nuclear lobes.

Eosinophiles are reduced in number, particularly during relapses ; basophiles usually disappear from the circulation, and monocytes are diminished.

As a good deal of our subsequent argument is based on the changes in the circulating blood, it is necessary to summarise them :—

(*a*) *The typical blood picture of pernicious anæmia :—*

Some anæmia, with colour index above unity.

Polychromasia, anisocytosis, poikilocytosis and punctate basophilia are present, but slight.

Leucopenia is present, and lymphocytes form about 50 per cent. of the leucocytes.

Monocytes and eosinophiles are reduced.

Normoblasts are very scanty, and megaloblasts, although usually rather more numerous, are difficult to find.

(*b*) *The blood picture during gradual recovery from a relapse :—*

Much polychromasia, poikilocytosis, anisocytosis and punctate basophilia.

Leucocytes rising, and lymphocytes relatively decreasing.

Nucleated red cells (mainly normoblasts) numerous, but diminishing.

(*c*) *The blood picture during rapid recovery from a relapse :—*

Very much polychromasia, poikilocytosis, anisocytosis and punctate basophilia.

Mainly nucleated red cells (mainly normoblasts).

Transient leucocytosis.

Reduction of the relative number of lymphocytes occurs very rapidly.

(*d*) *The blood picture in very severe cases :—*

Little polychromasia, poikilocytosis, anisocytosis and punctate basophilia.

Nucleated red cells of both types very scanty, but normoblasts often appear in large numbers just before death.

Extreme leucopenia, and great relative lymphocytosis.

Eosinophiles and monocytes very much reduced, and may even be absent.

It cannot be too strongly emphasised that *megalocytosis* is the most important diagnostic feature of the blood in pernicious anæmia, and may be present at a time when no manifestations of the disease are clinically appreciable.

Another invariable character of the blood is found in the persistent reduction in the number of **Blood-platelets**; these rise towards normal during remissions, but never attain their proper level; and during relapses well-marked reduction to quite low figures is usual. This fact may often be of great diagnostic value in cases in which remission is very complete, and the amount of megalocytosis is very small, because the platelets never return to normal numbers.

Briefly it can be stated that, except in the most severe cases, there is evidence in the circulating blood of vigorous formative activity, which is partly normal in type (normoblastic), but, in part, abnormal (megaloblastic).

A most striking feature of the disease, which does not disappear during remissions, is **Achylia Gastrica.** Hurst attributes a good deal of importance to this condition because he presumes that the absence of acid from the gastric juice permits the entrance of bacteria into the small intestine, and to organisms so introduced he attributes the most important ætiological function. Various types of bacteria have been blamed, but Hurst regards streptococci as being the most important. Meesen has described a small spirochæte in the gut and even in the blood, but its existence has never been confirmed.

In this connection it is important to recollect that achylia

gastrica is by no means a rare condition in persons who are otherwise healthy; there seems to be no doubt that the incidence of constitutional achylia is abnormally high in the relatives of sufferers from pernicious anæmia. Zadek reports examinations of 49 relatives of 20 cases of the disease; he found 3 persons with complete achylia and absence of pepsin as well as acid, 7 with no acid, 15 with small amount of acid, 9 with hyperchlorhydria, and 15 with normal gastric juice.

Weinberg has pursued this line of investigation still further by examining the blood of persons with familial achylia gastrica. He gives details of 10 cases; 3 of these were close relatives of sufferers from pernicious anæmia, but appeared to be in normal health at the time of examination. The other 7 cases gave no history of pernicious anæmia in the family.

The first case showed 4,296,000 red corpuscles per cubic millimetre, 102 per cent. of hæmoglobin, and therefore a colour index of 1·2. There was no leucopenia.

The second case showed 4,116,000 red corpuscles per cubic millimetre, 108 per cent. of hæmoglobin, and a colour index of 1·18.

The third case showed 4,980,000 red corpuscles per cubic millimetre, 117 per cent. of hæmoglobin, and a colour index of 1·05.

In the seven cases with no family history of pernicious anæmia he found the colour index slightly above unity, slight megalocytosis and scanty platelets.

Presumably no one would care to call any one of these cases pernicious anæmia, but nevertheless the resemblance between their blood pictures and that of the real disease is very striking; in fact, only the absence of an appreciable degree of anæmia prevents the diagnosis from being made with considerable confidence.

The importance of Weinberg's observations is even more obvious when it is realised that a *familial incidence* of per-

nicious anæmia is quite common. Meulengracht, in particular, has thrown light on this occurrence by his record of five cases in one family in two generations. There were five brothers in the first generation, and four of these suffered from pernicious anæmia, while the son of the one brother, who appeared to be healthy, also had the disease. Such a mode of inheritance is quite common in a variety of nervous diseases ; a fact of peculiar interest when the frequency of nervous disorder in pernicious anæmia is remembered.

The discovery of a tendency to familial incidence in pernicious anæmia naturally led to the tentative presumption that the disease occurred exclusively in specially predisposed persons, and, as will be shown later, there are considerable grounds for supposing this to be the case.

The conception of a special *constitutional pre-disposition* to the disease is supported by certain observations relating to Bothriocephalus anæmia. It is well known that *infestation with the broad tape-worm* (Bothriocephalus latus) causes in some people an anæmia which is indistinguishable from pernicious anæmia. The striking fact is that only a very small percentage of the persons infested with this worm develop this form of pernicious anæmia ; and there are no differences known to exist between the worms in the pernicious and in the non-pernicious cases. The difference must, therefore, be sought in the host. It is very characteristic of Bothriocephalus pernicious anæmia that cure follows expulsion of the worm, but Schaumann has been able to observe and record cases in which such cure was followed many years later by the occurrence of relapses of typical " pernicious " character not accompanied by any infestation. He was also able to show that typical cryptogenetic pernicious anæmia may occur in the relatives of persons infested with the broad tape worm ; this seems to be additional support for the view that a constitutional factor is of great importance in the genesis of the malady.

It would be expected that, if achylia gastrica permitted

entrance of bacteria into the intestine, organisms would be found in the duodenal juice, but Zadek was never able to find traces of their presence. The only notable abnormality of the duodenal contents is the presence of a great excess of bilirubin, particularly during relapses.

No importance can be attached to the occasional reports of parasites in the fæces, with, of course, the exception of Bothriocephalus latus ; but there is great interest attached to the estimation of the amount of urobilin. Zadek states that the normal amount of urobilin does not exceed 25 mg. per cent., but in pernicious anæmia figures as high as 500 mg. per cent. have been found. This great increase in the amount of urobilin can justifiably be taken as evidence of greatly increased blood-destruction in the body.

The urine also contains considerable excess of urobilin which causes a dark coloration. Albumen is usually present, but is practically always scanty.

The **Histological Changes** in pernicious anæmia require description, not only because they throw light on the morphological basis of the constitutional peculiarity, but also because they illuminate the nature of the disease implanted on the predisposed soil.

One of the best known morbid changes is the deposition of ferruginous pigment in the liver. Hunter regards the existence of this hæmosiderosis of the liver as a strong support for his view that in pernicious anæmia the essential pathological process is hæmolysis in the portal area ; the blood-destruction is supposed to be due to bacterial agency. Such a view is not supported by the negative therapeutic results obtained by administration of intestinal disinfectants. Further, M'Master, Rous and Larimore have shown conclusively that hæmolysis need not be limited to the portal circulation in order to result in hepatic siderosis.

There can, of course, be no doubt that hæmolysis does occur in pernicious anæmia, but Naegeli has never been able to observe evidence of blood-destruction in the periphera

circulation ; this is explained by Peyton Rous's observation that red corpuscles are destroyed inside cells of the reticulo-endothelial system. The intensity of the hæmolysis varies very greatly at different times in the same case, which would scarcely be likely if the disease were due to a persistent production of hæmolysins by intestinal bacteria.

It has already been mentioned that many of the red corpuscles in the circulation in pernicious anæmia differ very markedly from normal, and it seems justifiable to presume that, when the spleen is presented with such abnormal elements, its cells will attack them. We know that in hæmolytic jaundice, splenectomy results in total disappearance of symptoms, although the abnormality of the red corpuscles persists ; the great decrease in the intensity of hæmolysis can only be the result of removal of the main destructive organ. There seems to be good reason for supposing that the excessive blood-destruction in hæmolytic jaundice is due simply to the activity of the spleen in disintegrating the abnormal corpuscles. In pernicious anæmia the red corpuscles are even less like normal elements than in hæmolytic jaundice, and it seems safe to conclude that their destruction is brought about in a similar way, *i.e.*, the hæmolysis in these diseases is a cellular rather than a humoral one.

The hæmosiderosis must obviously be regarded as the result of deposition of iron derived from the break-down of red corpuscles, but we are still faced with the problem of the disposal of the other constituents of the corpuscles. A considerable amount of phospho-lipin is contained in red corpuscles ; and it is difficult to suppose that the liberation of this material is not the direct cause of the intense fatty change found in the liver and other organs in this disease, *i.e.*, both the hæmosiderosis and the adiposis of the liver result from the storage of the products of destruction of red corpuscles. If the hæmolysis of pernicious anæmia were due to some unknown bacterial hæmolysin, it would scarcely be likely to result in stimulating the normal mechanism for

storage; and indeed it is hardly probable that only normal products would result from the lysis. McGowan has shown that in the livers of leucotic fowls one may find iron and fat in the same cell, and we are, more than ever, forced to the conclusion that both substances have a common origin. It is even probable that the apparently well nourished state of most sufferers from pernicious anæmia depends upon storage of the excessive amounts of phospho-lipins and fats liberated by the intense hæmolysis. We have, therefore, to presume that the difference between normal hæmolysis and that occurring in pernicious anæmia is only a quantitative one.

We cannot, however, accept the view that hæmolysis is the central fact of the disease, because in stages of complete remission there may be no evidence of any excessive blood-destruction.

Many writers have supported the view that hæmolysis is the essential feature of the malady; for example, Türk contended that the *pigmentation* which so very commonly accompanies pernicious anæmia was due to injury of the adrenal medulla by the anæmia. Unfortunately for this conception, there can be no doubt that in many cases the pigmentation is present for months or even years before the onset of anæmia (Schucany). The distribution of the cutaneous and mucosal pigmentation is identical with that seen in Addison's disease, and there can be but little doubt that it results from a similar lesion, viz., of the suprarenal cortex, but there is scarcely sufficient evidence to support the view of Stephan that the disease itself is due to adrenal insufficiency.

Other evidence of endocrine disturbance is not common, but polyuria is not rare, and according to Schaumann is present in Bothriocephalus anæmia, and persists even after expulsion of the infesting worm.

The morbid changes in the *bone marrow* have naturally attracted much attention, but it can scarcely be claimed that

their nature is understood. In all cases there is much increase in the amount of myeloid tissue in the long bones, which are often completely filled with red formative marrow, but almost invariably this hyperplasia is most intense in the upper parts of the proximal long bones, and least marked in the distal bones of the limbs.

The histological appearances, as would be expected, indicate the presence of very active erythropoiesis. Immature leucocytes vary in number, but eosinophiles are almost always fairly plentiful. Megakaryocytes are scanty, as would be expected when the thrombocytopenia in the blood is remembered. There are always a very large number of non-granular basophilic cells about the nature of which unanimity has not yet been reached. Naegeli contends that they are myeloblasts, but it is difficult to understand why the myeloid stem-cells should become hyperplastic in an anæmia. It is more rational to agree with Ellermann that they are, as a rule, very immature erythroblasts (erythrogonia).

It is difficult, even in the normal marrow, to distinguish the boundaries of the blood channels, and in a condition like pernicious anæmia, where there is great hæmatopoietic activity on the part of this reticulo-endothelium, it is often almost impossible. Nevertheless, I feel convinced that it is possible to determine that these large non-granular cells always lie in an intra-vascular position. It has already been stated that erythropoiesis is always an intra-vascular process, while leucopoiesis is extra-vascular; it is, therefore, clear that these cells must be erythroblasts. Further, I am convinced that, even in the most immature of these cells, it is possible to distinguish a " cart wheel " arrangement of the nuclear chromatin; they must, therefore, be regarded as being very young normoblasts.

The number of leucocytes per unit area of marrow is definitely decreased, but the huge proliferation of myeloid tissue in all the bones makes it probable that the total number

of leucocytes in the marrow of all the bones is no less than normal, but why they do not appear in the circulation in normal numbers cannot yet be explained.

There is but little change in the *spleen* except evidence of increased erythrophagocytosis, which naturally varies in intensity according to the stage of the disease ; being most marked during relapses, and least noticeable during remissions. The greater part of the blood destruction seems to be due to the activity of the lining cells of the pulp spaces (histiocytes, reticulo-endothelium). The decrease in the amount of erythrophagocytosis accompanying remissions is also associated with decrease of the hyperplasia of the marrow, which may return practically to its normal extent (Zadek). I have personally no doubt that megalocytes are present, even if in very small numbers, during remissions, but Zadek states that this is not the case, and that all the red corpuscles may be indistinguishable from normal in very complete remissions. In any case we can safely state that the blood regeneration which is the immediate cause of the remission is normoblastic, not megaloblastic, in type.

It will be remembered that megaloblasts have already been described as being essentially embryonic cells, which, in fœtal life, are formed in small intra-vascular foci in the liver. These foci are entirely devoted to the formation of megaloblasts, which arise here without any admixture of leucocytopoiesis. At no stage of embryonic life is there evidence of formation of megaloblasts in the bone marrow, and, therefore, it is not surprising that the remissions of pernicious anæmia, which result from myeloid hyperplasia, are never due to increase in the number of megaloblasts. Nevertheless, the presence of megaloblasts in the circulation is never missed at some stage of the disease, and, bearing in mind the embryonic condition, it is only rational to examine the liver with a view to determining whether megaloblasts are formed there in pernicious anæmia just as they are in embryonic life.

Formation of megaloblasts is confined to the inside of the hepatic capillaries in fœtal life (for a short time, traces of it can be seen in the vessels of the body stalk); but normally all traces of megaloblastic tissue disappear before birth. It is impossible to conceive of any method by which megaloblastic tissue could be re-formed in post-natal life, because, as has already been described, it is of entodermal origin, unlike the normal adult hæmatopoietic tissue, which is mesodermal.

In all cases of pernicious anæmia, it is possible to find intravascular islets of pure megaloblastic tissue in the hepatic capillaries, and their arrangement is identical with that seen in the embryo. This condition is certainly not the same as the "myeloid metaplasia," which may often be seen in the peri-portal connective tissue, because this is a process resulting in the formation of both normoblasts and leucocytes. The intra-vascular process in the capillaries of the liver lobules is capable only of producing megaloblasts.

Even at this stage of our description some inferences can profitably be drawn from the facts available. It has already been pointed out that for a time the human embryo possesses two kinds of red blood cells. The one is of entodermal origin, and consists of large hæmoglobiniferous nucleated cells (megaloblasts), and their non-nucleated offspring (megalocytes). The other kind of red cell is the normoblast with "cart wheel" nucleus, which gives rise to the ordinary non-nucleated red corpuscle of the blood of extra-uterine life; these cells are of mesoblastic origin.

Megaloblasts with basophilic cytoplasm as well as more mature ones with more pyknotic nuclei and a greater content of hæmoglobin occur in the embryonic circulation until a fully hæmoglobiniferous cell with dense nucleus arises, and this, after loss of its nucleus, is the megalocyte. It is obvious that the megaloblast can be regarded as the ancestor of the megalocyte, but it is quite unjustifiable to imagine that it is an immature form of normoblast. We know that the most immature normoblasts have basophilic (immature) cyto-

plasm, whereas some megaloblasts have eosinophilic (mature) cytoplasm ; it is clearly impossible that a more mature cell can be the immediate ancestor of a less differentiated one.

The primitive blood-forming tissue undergoes gradual atrophy at the same time as the definitive normoblasto-granulocytic one increases in extent ; and, by the time that the latter is completely transferred to the bone marrow, there is no trace of the former to be found in any part of the body. It is difficult to escape the conclusion that these are correlated processes, although the nature of the regulation is uncertain. The atrophy of the one system and the hypertrophy of the other occur at a time when there is no nerve supply to the parts concerned, and we have, therefore, to postulate the existence of a chemical regulation. The occurrence of endocrine disorders in pernicious anæmia perhaps suggests a clue as to the nature of the chemical irregularity. Fig. 6 shows the appearances in the liver in a typical case of pernicious anæmia.

If the intimate correlation of the two processes of megaloblastic atrophy and normoblasto-granulocytic hypertrophy be admitted, it is difficult to avoid the conclusion that defect in one process must be associated with mal-development of the other. Further, it is obvious that, as foci of megaloblastic tissue are present in the liver in pernicious anæmia, there must be persistence of a remnant of this type of cell from embryonic life, *i.e.*, the process of atrophy has been incomplete. There should, therefore, if the present argument be correct, be morphological evidence of malformation of the myeloid tissue in this disease. Have we any evidence that this is really the case ? At first glance it seems that the answer is in the negative, because we already know that great hyperplasia of myeloid tissue occurs in this disease ; this scarcely seems to be compatible with the idea of a defective myeloid system. When we examine the blood, the appearances suggest another possible explanation. We have seen that the number of granular leucocytes is always

reduced ; the only explanation for this is that, although the amount of myeloid tissue in the body is enormously greater than normal, it must be functionally defective. Even the condition of the circulating red corpuscles indicates the

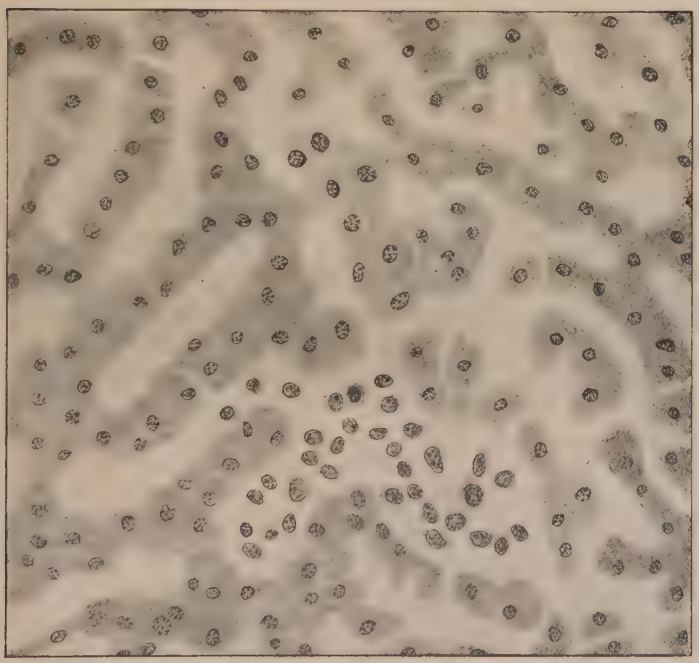

Fig. 6. –Liver from case of pernicious anæmia. (Reprinted from "Some morphological factors governing the incidence of pernicious anæmia." A. Piney. *Proceedings of the Roy. Soc. of Med.* (*Path. Sect.*), 1925, xviii.)

Intra-vascular formation of megaloblasts in one of the liver capillaries is distinctly seen (cf. figs. 4).

presence of defective marrow activity. Although there is ample evidence of active regeneratory processes in the formative organs, it is only irregularly and for short periods of time that the anæmia is overcome and the number of red corpuscles rises somewhere near normal (remission of the

disease). It is scarcely rational to attribute this peculiar defect of the marrow to the action of some unknown toxin, because it is impossible to conceive of a poison which would at one and the same time cause hyperplasia of the myeloid tissue, and yet inhibit another aspect of its functional activity. Further, if we agreed with Hurst that a toxin is at work, it would be necessary to postulate one which stimulated intra-medullary erythropoiesis while depressing leucocytopoiesis. In any case, it is impossible to suppose that a poisoned marrow could perform more work than a normal one for any considerable period of time.

As a working hypothesis, it may be accepted that in pernicious anæmia there is always persistence of a remnant of entodermal megaloblastic tissue, which would, in normal individuals, have disappeared before birth.

It is convenient here to interpose some account of the *neurological accompaniments* of pernicious anæmia. Meulengracht has given a very excellent account of the symptoms referable to involvement of the spinal cord. They may vary from the mildest of acro-paræsthesias to the most severe symptoms of sub-acute combined degeneration of the cord, and it is not necessary that the intensity of the nervous lesion should bear any obvious relationship to the degree of anæmia.

The important point, from the present aspect, is that nervous signs may long precede the onset of clinical manifestations of the disease; they may develop at the same time, but if absent before the onset of clinical pernicious anæmia, they do not develop into typical sub-acute combined degeneration after the presence of the underlying disease is obvious. If the nervous signs have been present in the prodromal stage, they may become much more severe during the progress of the malady, but they do not arise primarily after the disease has made its presence obvious.

The development of the peculiar neurological lesions is difficult to explain if we accept the view that pernicious

anæmia is due to the action of a toxin. We should have to imagine a variety of toxins, which vary in their strength in different cases. Such a multiplication of causes has not even the justification that Ehrlich's side-chain theory possessed, because, unlike that classical piece of invention, it cannot even stimulate further investigation, but must lead to sterility.

The histological changes in the cord affect the posterior columns to the greatest extent, but, in the lateral columns, the pyramidal and cerebellar tracts are involved; areas of affection of the anterior columns are not rare, but are always small. It is clear that we are not dealing with a "system disease" of the nervous system, but rather with a malady having a tendency to a systematic arrangement. The lesions are in the nature of focal degenerations, which show a well-marked tendency to coalesce into larger areas of tissue destruction. Lichtheim, in his original description of the disease, remarked upon the apparently recent character of the injuries, which was very surprising when it was realised that many of the cases were of very long duration. The appearance of newness of the lesions depends upon the absence of cicatricial (gliotic) processes around them.

It is difficult to imagine that lesions which cause no reaction on the part of the adjacent tissues, can be inflammatory in nature. If one postulates the action of a toxin, the difficulties are perhaps even greater. A toxin which in great concentration would cause focal degeneration in the spinal cord, would surely have an irritative effect upon the neighbouring tissue where it would be present in less concentration.

The characters of the changes in the spinal cord give the impression that they are due to abiotrophy in the sense used by Gowers, viz., defective formation, inasmuch as the tissues possess an abnormally low vitality, which is insufficient to last for a normal lifetime or to support them in disadvantageous circumstances, which normal tissues could and would counteract.

The frequency of occurrence of neurological symptoms is very great (although many cases are very mild); it was stated by Woltmann that they occurred in over 80 per cent. of cases. Histological lesions are found in the spinal cord in a slightly greater percentage.

From the more immediately practical aspect, the important question is that of diagnosis of pernicious anæmia in cases of sub-acute combined degeneration of the spinal cord in which no clinical signs of pernicious anæmia are present. The only safe rule is to perform an examination of the blood in all such neurological cases, even in the absence of clinical indications. I have seen a case in which there were 4,500,000 red corpuscles per cubic millimetre, 101 per cent. of hæmoglobin, and a colour index of 1·12; the leucocytes numbered 6,500 per cubic millimetre. The patient, who at that time showed the clearest possible clinical evidence of sub-acute combined degeneration of the cord, did not, in any way, suggest the clinical diagnosis of pernicious anæmia. Nevertheless he died with the typical clinical and hæmatological signs of this disease within three years of the first blood examination.

Hunter, as is very widely known, has attached enormous importance to the occurrence of *lesions in the tongue* of sufferers from pernicious anæmia. He has drawn far-reaching conclusions as to diagnosis and ætiology from the phenomena of this "glossitis." He postulates the presence of an infection in the gastro-intestinal tract, with its first site of incidence in the tongue, as being the cause of pernicious anæmia. The symptoms referable to the tongue may precede the onset of anæmia for a very considerable time, but, unfortunately for the conception of pernicious anæmia as a specific disease, similar glossitis may occur in other maladies. Sakheim states that glossitis does not occur either in Bothriocephalus or syphilitic pernicious anæmia, which, as has already been mentioned, are not otherwise distinguishable from ordinary cases of the disease. It is quite

justifiable to admit the possibility of an infective agent invading the body after primary infection of the tongue, but it cannot be denied that there is excellent evidence that other causes of pernicious anæmia exist. The conclusion that this malady is a pathological and clinical entity, but not an ætiological one, is difficult to resist.

The conception reached at this stage of the present account is that pernicious anæmia is a disease with a characteristic blood picture, but in which anæmia is not, at all times, an essential feature and may indeed be absent for quite long periods of time. The anæmia, when present, is to be regarded as the result of excessive hæmolysis by cellular means together with defective erythrocytopoiesis. Even in periods when the patient is free from anæmia, there is evidence of defective myeloid function in the persistence of leucopenia and relative lymphocytosis. The main characteristic of the blood picture is the presence of a variable degree of megalocytosis ; and we have already discussed the origin of the large corpuscles, and reached the conclusion that they are persistent representatives of certain intra-vascular cells of the embryonic liver. The atrophy of megaloblastic tissue, which normally is complete before birth, must obviously have failed in cases of pernicious anæmia. Further, it is contended that atrophy of megaloblastic tissue and development of the adult normoblastic-granulocytic system are correlated processes ; and that, therefore, if the one is incomplete, the other will necessarily also be ill-formed.

It is thus obvious that pernicious anæmia can occur only in such persons as have a remnant of megaloblastic tissue in their livers. The blood picture in this disease can, therefore, be said to have undergone reversion to " embryonic type," but this must not be taken to imply that the whole process of hæmatopoiesis is embryonic in character.

Such a view of the disease as a pathological process superimposed on a congenital malformation is supported by our knowledge of the fairly frequent familial incidence and also

by the fact that achylia gastrica, which is invariable in pernicious anæmia, also commonly occurs in several members of one family.

The view here adopted is that certain persons with a demonstrable morphological malformation can, in various circumstances, develop the signs and symptoms of pernicious anæmia. There are just a few known causes of the malady, *e.g.*, infestation with Bothriocephalus latus, syphilis, but the very great majority of cases are of unknown origin. In spite of this lack of accurate knowledge, it is useful to attempt to make some sort of classification of the cases :—

1. *Cryptogenetic cases*, which can be regarded as being due to some injury of the hæmatopoietic tissue, or to some added strain, in persons possessing the suitable "Anlage." Probably many of the noxa, capable of producing a secondary anæmia in normal persons, will produce pernicious anæmia in the predisposed.

2. *Infective cases* are those in which a definite parasite can be demonstrated to have excited the signs of the malady ; the obvious example of this type of case is Bothriocephalus anæmia. Here expulsion of the worm results in cure, which is often complete and permanent. Streptococcal infections, in the sense of Hunter, might also be included as probable members of this group, but the failure to effect cure by treatment of the infection makes for caution.

3. *Metabolic cases* would be those in which the signs of pernicious anæmia occur in association with such a condition as pregnancy, which is known to throw a strain on normal hæmatopoietic tissues and might, therefore, be expected to effect more intense alteration of congenitally defective ones.

4. *Cases associated with infection*, such as syphilis, need to be put into a separate group, because it seems as if the effect on the blood-forming tissue is not a direct action of the infective agent.

5. *Idiopathic cases* are included in a group, which will presumably decrease in size as our knowledge grows, but it

seems to be highly probable that the degree of failure of atrophy of the embryonic megaloblastic tissue varies in different potentially pernicious anæmic persons. If this be the case, we can well imagine that in some persons the development of the normoblasto-granulocytic system will be so defective as to prevent it from performing normal function for the whole of a normal lifetime. It is, thus, quite possible that the signs of pernicious anæmia might arise as a manifestation of a premature senility of an ill-formed myeloid system.

6. *Atypical cases* occur, and support the contention that the degree of congenital defect varies in different predisposed persons. Many of the cases of pernicious anæmia occurring during pregnancy relapse only if another pregnancy occurs ; this suggests that, in the absence of any special strain, the myeloid tissue can carry on its function, *i.e.*, the amount of defect must be small and the remnant of megaloblastic tissue left over from embryonic life can only be minute.

It may be objected that the characteristic blood picture does not represent the whole of the symptomatology of pernicious anæmia ; achylia gastrica and sub-acute combined degeneration have already been mentioned. The former condition is not known to depend upon any demonstrable structural change in the gastric mucosa ; and the latter has the characters of a pure degeneration with no effects upon even the immediately adjacent nervous tissue.

It has not been entirely the fault of medical men that they have neglected the observations built up on the foundations laid by Mendel, the famous Abbot of Bonn ; problems of human heredity are too complex and too little susceptible of adequate control to be of much use in interpretation. We can, nevertheless, look through the astonishing results obtained by the labours of the patient investigators of heredity to see whether any of their data or theories can, without undue straining of the conditions, be applied to man. It is known that all characters of a species are con-

trolled, in their development, by definite factors, which can be passed on from parent to offspring; further, it is recognised that an enormous number of characters are inherited by means of unit-factors. Mendel's original view that unit-factors are inherited singly has had to be modified, for it is clear that unit-factors are inheritable in groups. Factors in separate groups are independently inherited, but those of the same group are linked together, although the linkage is far from an absolute one. The number of groups appears to be constant for each species. It seems obvious that any alteration of a unit-factor must carry with it some effect upon the other factors of its own group; in breeding experiments it is found that alteration of one unit-character is associated with other changes. It seems justifiable, as a working hypothesis, to presume that the alteration of the character "fully developed normoblasto-granulocytic tissue" is inevitably associated with changes in the characters "atrophy of megaloblastic tissue," "full maturation of gastric function," and "normal formation of central nervous tissue." The contention here made is, therefore, that these are correlated abnormalities. Briefly, pernicious anæmia is regarded as a malady, due to a variety of causes, occurring only in such persons as have a particular type of hæmatopoietic system. It is not, as a rule, a "primary" anæmia, but probably represents the effect of agents, which in normal persons would induce only a simple anæmia.

We must not rest content with the present view of the nature of the pernicious anæmic process, and, in common fairness, must refer to some of the other conceptions which have been published.

Probably no one could be found to deny that excessive hæmolysis is present during the active stages of pernicious anæmia, but there are many who would object to the view that this occurrence is a sufficient explanation of the phenomena of the disease.

The existence of certain resemblances between pernicious

anæmia and sprue have recently attracted attention; unfortunately no details are available, but it has to be remembered that sprue is due to a fungus, Monilia albicans; and this again supports the view of Hurst that intestinal infection is very important in pernicious anæmia. It must be emphasised that, although many different bacteria have been regarded as being the "specific" cause of pernicious anæmia, there is not one of them that has been found in a large series of cases; the longest series is that of Hurst, who found streptococcus longus in the duodenal juice of all his cases of the disease; but he also found the same organism in 11 per cent. of his controls.

The idea that the hæmolysis of the disease is due to blood destruction in the portal area is widespread, but, as has already been mentioned, it cannot be supported simply by the observation that hæmosiderosis is most intense in the liver. Cederberg has shown that some hæmolysis occurs in animals dying of anaphylactic shock, and supposes that the blood destruction in pernicious anæmia may be the result of anaphylaxis arising as the effect of absorption of foreign protein from the gut. Faber has followed up this idea, and claims that in some cases he has seen good results in the treatment of pernicious anæmia from gradual desensitisation to various proteins.

It is interesting to mention the work of Iwao at this juncture. This writer found that an anæmia very like pernicious anæmia could be produced in animals by injection of p. oxyphenylethylamine. The point of importance is that this substance, which is also known as tyramine, can be produced from cheese by the action of B. coli. It is suggested by Seyderhelm, Lehman and Wichels that this toxin can arise in the small intestine if the flora becomes the same as that of the colon. Attractive though the theory may be, it is not of great value until it has been shown that anæmia due to tyramine is really identical with pernicious anæmia. These same writers state that the flora of the small intestine

can be made identical with that of the colon, in dogs, by experimental production of stenosis of the ileum ; if this is done, anæmia develops. Meulengracht has been able to observe and record five human cases of pernicious anæmia in which a stricture of the intestine was found. It does not really seem that such findings in any way nullify the conclusion previously reached that a variety of causes can produce the disease in predisposed persons.

There are certain chemical observations which, while not explaining the genesis of the malady, may throw considerable light on the method of the hæmolysis.

Eppinger and King have shown that there is some relationship between the amount of hæmolysis and the degree of unsaturation of the fatty acids of the blood ; and Csonka describes an invariable increase in the iodine number of the blood fats in pernicious anæmia. Bloor went even further by showing that there was not only an increase in the degree of unsaturation, but also an increase in the amount of fatty acid. When these facts are brought into relationship with the observations of Faust and Tallquist that oleic acid and its salts are more hæmolytic than is stearic acid and its salts, we seem to get some light thrown on the mode of hæmolysis in the disease under discussion. Further, splenectomy is followed by decrease in the amount of unsaturated fatty acid, and by an increase in the cholesterol-content of the blood.

The **Treatment of Pernicious Anæmia** is still far from satisfactory, but some improvements can be recorded. The use of arsenic is still widespread, and is very valuable. It is interesting to inquire into the mode of action of this drug. In order to estimate the value of any substance in stimulating erythropoiesis, it is clearly necessary for us to possess some criterion of youthfulness in circulating corpuscles. We have such a guide in the presence of " reticulated " corpuscles in the circulation.

These elements are characterised by the possession of a fine

reticulum in their substance, as is demonstrable with vital staining (Appendix I.). Normally there are between 0·5 and 2 per cent. of these corpuscles in the blood (Engel), and one would expect that any substance causing excessive erythropoiesis would result in an increase of these elements in the circulation. Pernicious anæmia is a malady in which the marrow works abnormally, and even without treatment there are many reticulated red corpuscles in the circulation. These are not quite identical either with the reticulated corpuscles normally present or with those that occur after hæmorrhages ; these latter are more resistant to the action of hypotonic solutions of saline than are normal corpuscles, whereas the reticulated corpuscles occurring in untreated pernicious anæmia are definitely defective in resistance (Buckman and MacNaugher).

There is no doubt that the administration of arsenic in pernicious anæmia increases the number of reticulated corpuscles of normal character in the circulation, and at the same time reduces the amount of hæmolysis, as evidenced by the disappearance of bilirubin from the blood serum. The stimulating effect of arsenic on hæmatopoiesis is obvious, but there is excellent evidence that it does not act on the bone marrow, at any rate, directly (Weiss). The administration of iron in post-hæmorrhagic anæmias has a most admirable effect, whereas arsenic has no influence on the rate of regeneration. Weiss has no suggestion to make as to the mode of action of arsenic ; we can give no explanation either, but it seems possible that its site of action in pernicious anæmia is on the megaloblastic tissue in the liver.

There seems to be no special advantage associated with any particular arsenical product. Fowler's solution is still the most important preparation, but, in cases of intolerance of arsenic by mouth, injection of such preparations as arsacetin gives excellent results. I feel almost certain, although I have no demonstrable evidence, that treatment by injection sometimes gives good results when oral adminis-

tration has failed; this state of affairs may occur in patients who have previously responded well to the usual treatment.

The question of a suitable *diet* in cases of pernicious anæmia requires careful consideration. It is usual to recommend a dietary with a high nitrogen content and a high number of calories (Barker and Sprunt); this has at least one thing to support it, viz., the fact that patients have usually placed themselves on a deficient diet during their illness, and will, therefore, be benefited by a more generous supply of food.

There is some evidence that a diet rich in animal protein favours blood regeneration (Morawitz and Kühl); and an abundance of vitamins has a similar effect (Jencks). Whipple and Robscheit-Robbins have shown that liver is a valuable food in the regeneratory stage of post-hæmorrhagic anæmia; this may well be the result of its high protein content. Not all proteins are of equal value in supplying the factors necessary for active hæmatopoiesis; Smith and Moise have shown that gliadin, for example, is valueless in this respect.

An excess of fat is commonly held to predispose to undue fermentation in the intestine; this is so common a condition in pernicious anæmia that it seems only rational to reduce the intake of fatty articles of diet.

Minot and Murphy have made a careful study of the most suitable dietary for patients suffering from pernicious anæmia and give a detailed account of their results; they claim that remissions occur promptly after the assumption of the new diet, but have not yet obtained any evidence pointing to longer periods of freedom from relapses. They suggest:—

120 to 200 gm. of calves', beef or chicken liver.

400 gm. of fresh fruit.

125 gm. of red muscle meat (beef heart desirable).

Not less than 300 gm. of fresh vegetables (particularly spinach, asparagus, cabbage, lettuce and tomato).

Not more than 70 gm. of fat (avoiding cheese, bacon, fried food, cream and butter).

Sparing use of sugar.

Starchy foods to taste, avoiding grossly sweet foods.

Not more than 240 gm. of milk, and avoid excess of salt.

This represents the basis of the daily dietary suggested by these writers.

The dietetic treatment should be combined with ordinary medicinal measures when these are rendered necessary by the presence or suspicion of a relapse.

It has already been mentioned that Hurst attributes pernicious anæmia to a gastro-intestinal infection which is enabled to reach the gut by the absence of acid from the gastric juice. He therefore recommends the administration of dilute hydrochloric acid by mouth to sufferers from the disease. Patients as a rule object very strongly to this mode of treatment, and in any case, as according to Hurst, the infection has already settled in the intestine, the acidification of the gastric juice can be little more than a locking of the stable door after the horse has gone.

Surgical measures have been used in pernicious anæmia in a comparatively small number of cases; *splenectomy* in this disease gives temporarily good results, but cannot be regarded as representing a method of treatment to be used as a routine. Removal of the spleen of a normal patient results in morphological changes in the blood, which persist for a long time (Eppinger). Punctate basophilia, polychromasia, normoblasts and Howell-Jolly bodies in the red corpuscles together with an increase of eosinophile leucocytes and monocytes is a characteristic condition. There is no evidence of anything more than a transitory polycythæmia; this suggests that the removal of the spleen results in a hyperplasia of the remainder of the reticulo-endothelial system so that the rate of destruction of red corpuscles ultimately returns to normal.

Remissions of pernicious anæmia occur spontaneously in many cases, and in almost all can be brought about by administration of arsenic. When oral administration of arsenic fails, as it usually does after several relapses, it may be possible to induce further remissions by the use of preparations suitable for intra-muscular injection (arsacetin) or for intra-venous injection (novarsenobillon), although the latter method is not free from risk.

My own impression is that splenectomy in pernicious anæmia should be resorted to only in cases which will no longer respond to medicinal treatment. It may be necessary to perform blood transfusion before or immediately after the operation, but, if the surgical interference itself is not fatal, a remission may confidently be expected. I have, however, not often been able to observe recovery from a relapse in a splenectomised patient, *i.e.*, the remission induced by splenectomy is very often the last one.

We have now to discuss the possible relationship of pernicious anæmia to certain other diseases, such as leukæmia, because this is a matter which has recently been the subject of much discussion. The modern arguments on the theory have been stimulated by the discovery of Ellermann that the virus, which will produce leucosis in fowls, may in some specimens cause a pure anæmia, which he regards as being identical with pernicious anæmia. Although it is not clear that the leucosis of fowls is really identical with human leucosis, such a discovery is at least worthy of discussion.

When one compares a typical case of pernicious anæmia with an equally characteristic one of leukæmia there is, of course, very little resemblance, and it is not such diseases that we have to describe here. The question is whether there exist cases of leukæmia with so many signs characteristic of pernicious anæmia that we are justified in believing in the occurrence of transitional forms. Leube, in 1900, described the pathological condition to which he gave the name

"*leukanæmia*"; then, in addition, as has been mentioned, there are many writers who claim to have found a close relationship between pernicious anæmia and sepsis, while an even larger number believe in a similar relationship between the leucoses and sepsis. There is obviously a possibility that more than superficial resemblances exist between pernicious anæmia and leukæmia.

A case, which was recorded by Hoff, shows light on the subject, and is worthy of more detailed reference.

His patient was a woman, aged 28, who had had no noteworthy illnesses, but for the past two months had suffered from deafness and aural polypi. She suddenly started to run a high temperature, had pains in the limbs, and numerous vesicles on the legs. The blood picture showed 2,984,000 red corpuscles per cubic millimetre, 64 per cent. of hæmoglobin, and a colour index of 1·09. There were 25,300 leucocytes per cubic millimetre, and the percentage composition of the leucocytic picture was as follows :—

59·5 per cent. of neutrophilic polymorphonuclears.
5·0 per cent. of mature metamyelocytes.
2·0 per cent. of young metamyelocytes.
4·0 per cent. of myelocytes.
20·5 per cent. of lymphocytes ; and
9·0 per cent. of monocytes.

A fortnight later the colour index was 1·3, with 1,936,000 red corpuscles per cubic millimetre, and 52,300 leucocytes. Hoff states that a few megaloblasts were present ; and there seems to be no doubt that he had previously carefully made himself acquainted with the characters of these cells in the strictest sense. Later still myeloblasts were found in the blood. The histological changes in the tissues seem to have had the characters both of leucosis and of pernicious anæmia.

In a second somewhat similar case the colour index rose on several occasions to 1·6.

The question we have to answer is not whether leukanæmia is the name to apply to these cases, but what is the essential nature of the pathological process. Naegeli, for example, states that Leube's original case was neither leukæmia nor pernicious anæmia, while Pappenheim contends that leukanæmia is really always a leucosis.

In Hoff's two cases there was high colour index, well marked poikilocytosis and anisocytosis, megalocytes and megaloblasts, bilirubinæmia, achylia gastrica, "thrush breast" striation of the myocardium, and hæmosidersosis. We cannot escape the impression that these are conditions very closely simulating pernicious anæmia.

It must not be supposed that Hoff's cases are isolated examples of their kind in modern literature.

Ullmann and Weiss recorded a case, which, in its early stages, had all the characters of pernicious anæmia, but later became converted into an equally typical case of acute leukæmic lymphadenosis.

The case which Brucke described is of particular importance. The diagnosis was aleukæmic lymphadenosis, but there were several characteristic signs of pernicious anæmia, viz., high colour index, megalocytes in the blood, a megaloblast in the blood on one occasion, achylia gastrica, signs of sub-acute combined degeneration of the spinal cord, and glossitis in the sense of Hunter.

Even in typical cases of pernicious anæmia there are some resemblances to leucosis, *e.g.*, Naegeli states that the non-granular cells so numerous in the marrow of cases of pernicious anæmia are certainly myeloblasts; and, indeed, myeloblasts may often be found in the blood, even if only in very small numbers (Hoff).

Writers like Naegeli, who deny the existence of such mixed cases, interpret the case of Meyer-Ruegg as one of pernicious anæmia associated with sepsis, although there were 30,000 leucocytes per cubic millimetre, and 25 per cent. of them were myelocytes!

It may be objected that, if the existence of mixed cases be admitted, it is not possible to adhere to the view previously stated that pernicious anæmia occurs only in predisposed persons. My own opinion is that the very existence of transitional forms between leukæmia and pernicious anæmia is strong support for my conception of the disease. The

majority of sufferers from the leucoses do not show any signs of pernicious anæmia, and surely it is possible that those who do show the signs are ones who possess the peculiar mal-formation. It has already been stated that a variety of agents may cause pernicious anæmia in predisposed persons, and it is difficult to see why the strain on the hæmatopoietic tissues imposed by a leucosis should not be sufficient to make the latent "pernicious" tendency manifest itself. This seems the more probable when it is remembered that achylia gastrica occurs in all cases of pernicious anæmia, and has not been found absent, so far as I am aware, in any "mixed case" whose gastric juice has been examined.

Before summarising the contents of the present chapter it is necessary to discuss the vexed question of the occurrence of true megaloblasts in the blood in diseases other than pernicious anæmia. Naegeli and his followers contend that these cells are absolutely pathognomonic of pernicious anæmia, although they regard the disease as being of varied ætiology. It is, therefore, necessary for them to believe that a variety of toxins can cause this particular type of blood-regeneration, because they do not agree that the megaloblast is derived from a special organ in the embryo, and from an embryonic rest in cases of pernicious anæmia.

It is not surprising that the older writers, who did not possess modern nuclear stains of anything like the quality that we possess, should have tended to diagnose far too many megaloblasts because they were forced to take the size of the cell as the most important criterion. This does not apply to modern writers, and, when such an authority as Hirschfeld states that megaloblasts occur in the blood in leukæmic myelosis, we can scarcely doubt that he is referring to megaloblasts in the strictest sense of the word. It is not only in cases of so-called "leukanæmia" that megaloblasts have been described in the blood, but also in other anæmic

states. Hoff has contributed to this subject by his description of a case of infantile anæmia :—

The child was four months old and appeared to be anæmic. Examination of a blood film showed anisochromæmia, anisocytosis, poikilocytosis, polychromasia, and very definite megalocytosis. The differential count showed 1·3 per cent. eosinophiles, 0·4 per cent. myeloblasts, 1·8 per cent. myelocytes, 4·3 per cent. other neutrophiles, 91 per cent. lymphocytes, 2·2 per cent. monocytes. Six megaloblasts were seen while counting 300 leucocytes; eight normoblasts were also seen, and Jolly bodies were numerous.

The child had been a full-term infant and was suckled for two months, but was then given diluted goats' milk.

On examination there were a number of slightly enlarged superficial lymphatic glands in the neck and groins. Both liver and spleen were much enlarged and hard. No urobilinuria or urobilinogenuria. Wassermann reaction was negative. The more detailed examination of the blood which was possible after admission to hospital showed 1,665,000 red corpuscles and 7,600 leucocytes per cubic millimetre, hæmoglobin 37 per cent. and colour index 0·95. The differential count showed 1 per cent. eosinophiles, 0·6 per cent. myeloblasts, 2·3 per cent. myelocytes, 17·3 per cent. other neutrophiles, 78·5 per cent. lymphocytes, and 0·3 per cent. basophiles.

In two months the child became perfectly well, and the liver and spleen were no longer enlarged.

The genesis of such a case would have been quite obscure until the publication, by Scheltema, in 1916, of his observations on infantile anæmias due to goats' milk (see also Alimentary Anæmia, p. 247). It has often been suggested that the anæmia occurs as a result of administration of goats' milk only if some special constitutional peculiarity is present, but the case cited above recovered with no treatment other than replacement of the goats' milk by a more suitable diet. It must be presumed, therefore, that goats' milk has some directly damaging effect, as was claimed by Beumer and Wieczoreck. Stoeltzner states that the power of goats' milk to cause anæmia is due to the absorption of high molecular fatty acids from it.

Hoff publishes drawings of the cells, which he regards as megaloblasts in this case, and they certainly seem to have the characters which I have described elsewhere.

There are, of course, two methods of dealing with the matter. One may categorically state, as Naegeli does, that any case in which megaloblasts are found in the blood is definitely pernicious anæmia, or one can attempt to find some unifying principle to include all the cases in which megaloblasts are found in the blood in persons who show little other sign of pernicious anæmia. It is an obstructive tendency, which has manifested itself of late in hæmatology, to try to produce rigid systems of classification because, after all, the variety of stimuli capable of affecting the hæmatopoietic tissues is much greater than is the number of possible modes of reaction ; therefore identical reactions can result from widely different stimuli.

If our account of the history of the megaloblast in the embryo is correct, we should immediately have an explanation of the rarity of occurrence of megaloblasts in the hæmic reactions to stimuli other than that of pernicious anæmia. It has already been contended that a variety of causes, acting on persons possessing the requisite remnant of entodermal megaloblastic tissue, can produce pernicious anæmia. It seems to be highly probable that other stimuli to the hæmatopoietic tissues of such persons would cause the appearance of megaloblasts in the blood ; this would account for their occurrence in cases of leucosis, and would adequately explain why they are present in such a very small percentage of cases. The condition in infants is perhaps rather different ; it has been stated that normally all trace of megaloblastic tissue disappears from the body before birth, but it is quite conceivable that there may occasionally be persistence of a remnant of this tissue. Such a remnant may be of future importance if it does not undergo atrophy at an early date, because it will then form the morphological basis of the constitutional tendency to pernicious

anæmia. It is equally possible that such a small remnant, which should have disappeared before birth, may atrophy within the first few months of life. If, however, an infant with such a remnant is exposed to a noxious stimulus such as goats' milk, megaloblasts may appear in the blood, although, after recovery, complete atrophy of the megaloblastic tissue may take place, and the child no longer possess the morphological sub-stratum of pernicious anæmia.

The position we have, therefore, to take up is that the presence of megaloblasts in the blood is indicative of the persistence of megaloblastic tissue, *i.e.*, the possession of an " Anlage " from which, with certain non-specific stimulation, pernicious anæmia may develop. This is obviously not quite the same as Naegeli's statement that the presence of megaloblasts in the blood is pathognomonic of pernicious anæmia.

In the present conception of pernicious anæmia it must continually be borne in mind that two factors are essential, viz., a constitutional abnormality and an external stimulus. As a rarity, it is possible that a constitutional anomaly alone may be sufficient to produce the typical signs of the disease, if the hæmatopoietic tissues, which are primarily ill-formed, wear out during a normal length of life.

It cannot be, and is not claimed that a complete explanation of the genesis of pernicious anæmia has been supplied, but it is felt very strongly that a certain amount of order has been introduced into a somewhat chaotic subject.

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CHAPTER V

LEUKÆMOID BLOOD PICTURES

I. Infective

The term "leukæmoid blood pictures" is applied to those alterations in the circulating blood which resemble the blood picture of the leucoses without, however, having as their substratum true leucotic changes. The essential factor in the development of the leukæmoid pictures is a reactive process; in the majority of the cases a definable causative agent is at work. This chapter will embrace the description of leucocytosis in its widest sense, for there is no sharp distinction to be made between the blood picture in infective conditions and that in the leucoses; the differences are to be found only in the formative tissues.

Leukæmoid blood pictures occur in association with the majority of infections at some stage in their development, but the hæmic changes are often comparatively slight. The majority of bacterial infections (probably all of them) are associated with very definite alterations, both in the quantitative and the qualitative characters of the blood picture. Most infections are accompanied by an increase in the number of circulating leucocytes (leucocytosis), which, in acute cases, depends entirely upon addition to the neutrophilic granular cells (neutrophilia); this occurs at the same time as a reduction in the number of eosinophilic cells, and, in many cases, of monocytes. These are, as Arneth has very justly observed, all quantitative variations. The more important aspect of the alteration is to be sought in changes in the types of circulating cells, a subject to which Arneth has made important contributions.

It is necessary just to repeat that the normal development of the neutrophilic polymorphonuclear leucocyte is from a mono-nuclear cell (myelocyte) with a simple round nucleus ; the intermediate stage is a cell with a single indented nucleus, but with no true nuclear lobulation ; this is the meta-myelocyte. It is obvious that the cell with a simple round nucleus is younger than that with the indented one, and this form is, in turn, younger than the true polymorphonuclear element. Arneth has pursued this line of thought further by contending that a polymorphonuclear cell with only two lobes is younger than one with three, and so on. He states that normally the percentage of each type of neutrophilic cell in the circulation varies only within narrow limits. He divides the cells with neutrophilic granulations into five groups, viz., those with only one nucleus (simple or indented), and those with two, three, four, and five or more nuclear lobes. In normal blood he states that the following figures are approximately correct :—

Class I., 5 per cent. ; Class II., 35 per cent. ; Class III., 41 per cent. ; Class IV., 17 per cent. ; Class V., 2 per cent.

He has carried his classification to an extreme degree of delicacy by subdividing each of the classes. Class I. is very naturally divided into myelocytes, metamyelocytes with slightly indented nuclei (W cells), and metamyelocytes with deeply indented nuclei (T cells). Further, he has pointed out that, in the true polymorphonuclear leucocyte, the shape of the lobes is variable ; there are two normal shapes, viz., a knob-like mass (K), and a bent S-like piece of chromatin (S).

In evaluating this " Arneth index " he examines 100 neutrophilic granular leucocytes and calculates the percentage of each kind. His full description of the " neutrophile blood picture " in health is as follows :—

Class I. :	Per cent.
M cells (ordinary myelocytes) . . .	*Nil.*
W cells	0·2
T cells	5·0

	Per cent.
Class II. :	
2 K cells (with 2 knob-like lobes)	0·27
2 S cells (with 2 S-like pieces)	23·46
1 K, 1 S cells	11·69
Class III. :	
3 K cells	2·27
3 S cells.	5·6
2 K, 1 S cells	16·66
2 S, 1 K cells	16·40
Class IV. :	
4 K cells	3·80
4 S cells.	0·07
3 K, 1 S cells	6·40
3 S, 1 K cells	1·60
2 K, 2 S cells	4·73
Class V. :	
5 K cells	1·00
4 K, 1 S cells	0·40
3 K, 2 S cells	0·40
4 K, 2 S cells	0·07
3 K, 3 S cells	0·07

These figures are, of course, the average of a large number of observations. I can quite confirm Arneth's statements as to the "index" as obtained in normal individuals. He claims that well marked re-arrangements of the grouping occur in disease; these are said to be characterised by decrease in the number of more complex nuclei with corresponding or excessive increase of the simpler types, which Arneth regards as being younger forms.

There is much dispute as to the correctness of the view that neutrophilic cells with many lobes in their nuclei are necessarily older than those with only two lobes, so that Arneth's interpretations are not widely accepted. The greatest difficulty arising in estimating the "index" in infective conditions is, however, not a theoretical, but a practical one. In the great majority of infections the neutrophilic granular cells bear the brunt of the battle with the bacteria, and many do not come unscathed from the ordeal.

Remnants of the least fortunate of the neutrophiles are seen in a most degenerate condition in pus ; it is not surprising, therefore, that even circulating neutrophile cells suffer some degree of injury, either as the direct result of their defensive activities or of the action of toxins. The " toxic " changes, which are seen in neutrophilic cells, in these conditions are those characteristic of cell injury in general. There is increased condensation of the nucleus (pyknosis) with obliteration, partial or complete, of its normal markings and form, loss of granules, and even vacuolation of the cytoplasm (Alder). The first-named change causes extreme difficulty in the estimation of the " Arneth index " in infective conditions, and may even render it impossible to make an accurate examination. It often becomes impossible to determine how many lobes a particular cell possesses, and so the confirmation of Arneth's statement regarding variations of the neutrophilic blood-picture is incomplete.

We owe a much simpler " index " to the work of Schilling, and this should become an indispensable method of clinical and pathological investigation. This author divides the neutrophilic cells into the following groups :—

Myelocytes, young metamyelocytes (with only the slightest indentation of the nucleus), older metamyelocytes (with deep indentation, but no true lobulation of the nucleus), and polymorphonuclears. In performing the ordinary differential count of leucocytes, each of these types is counted separately, so that, in the complete result, each variety of neutrophilic granular cell is expressed as a percentage of the total number of leucocytes ; in Arneth's method they are expressed only as a percentage of the total neutrophilic cells. Victor Schilling gives the following as normal figures for the leucocytic blood picture :—

Leucocytes, 6,000 to 8,000 per cubic millimetre.

Neutrophilic granular cells, 67 per cent. These are composed of 63 per cent. of polymorphonuclears and 4 per cent. of old

metamyelocytes (band forms); the young metamyelocytes (young form) is absent.

Eosinophiles, 3 per cent.; basophiles, 1 per cent.; lymphocytes, 23 per cent.; monocytes, 6 per cent.

It will be seen that in this method there is no need to take note of the number of lobes in the nuclei of the cells, and no " toxic " change, however severe, makes it impossible to recognise to which type a given cell belongs. Further, there is no doubt that the cells, in Victor Schilling's scheme, are arranged in order of maturity. A number of examples of the practical application of this " hæmogram " are given later, but one will be convenient here in order to have a concrete case for discussion. In a case of septic arthritis of the knee joint the following " *hæmogram* " was obtained :—

Leucocytes	10,000 per cubic millimetre.	
Eosinophiles	*Nil.*	
Basophiles	*Nil.*	
Lymphocytes	19 per cent.	
Monocytes	14 ,,	
Myelocytes	*Nil.*	Total neutrophile cells, 67 per cent.
Young forms of metamyelocytes	19 per cent.	
Band forms of metamyelocytes	17 ,,	
Polymorphs	31 ,,	

The features of this picture are leucocytosis of moderate degree, probably not sufficient by itself to justify a diagnosis of suppuration, absolute eosinopenia, which is very characteristic of active infection, and monocytosis, which is common, but not invariable in such circumstances. The neutrophiles show a very definite increase in the number of immature forms in the blood; the band forms are increased from the normal percentage of 4 to 17 per cent., and the young forms, which normally are absent from the peripheral blood, number 19 per cent. There is thus an obvious emigration of young neutrophilic cells from the marrow;

this is termed a "shift to the left" by both Arneth and Victor Schilling. Before we can usefully cite other examples some reference to the factors influencing the occurrence of leucocytosis of various types is essential, as is also a discussion of the theoretical bases of the process. It is not possible to draw definite lines between the various processes at work, but a classification is, nevertheless, valuable. I have previously attempted to make a simple and accurate arrangement of the known facts, and this is here reproduced in a slightly modified form in which leucocytosis and leucopenia are brought into close relationship with one another.

1. **Increased Functional Demand as a Cause of Neutrophilic Leucocytosis (Neutrophilia).**—A number of physiological states, such as digestion and pregnancy, in addition to the majority of toxic and infective conditions, can cause a well-marked leucocytosis. This may occur with astonishing rapidity without any sign of hyperplasia of the myeloid tissue, which must obviously contain a stock of mature cells to meet such demands. If the requirement for an excessive number of cells persists, hyperplasia of the marrow occurs, and a shift to the left of the neutrophiles will accompany it. In any infective malady a series of changes occurs in the composition of the blood picture. First there is extreme neutrophilia with great reduction, or even disappearance, of eosinophiles and basophils, and reduction of lymphocytes. One gains the impression of a marrow so actively engaged in the production of one type of cell (neutrophilic leucocyte) that the other varieties receive little attention from the parent tissue, which we have already decided to be the reticulo-endothelium. This one-sided activity of the parent reticulo-endothelium also manifests itself in a reduction of intensity of lymphocytopoiesis below normal limits. Well-marked hyperplasia, and even macroscopic increase in extent of marrow, can be found at autopsy in chronic cases. This increase in amount of myeloid tissue has a definite effect upon the composition of the blood

picture; the relative neutrophilia tends to decrease, and the types of cells, which have been so much reduced or have entirely disappeared, are again found, although in numbers smaller than normal. These changes appear to depend entirely upon the fact that a sufficient amount of myeloid tissue is available for all purposes, and not only just enough to produce the protective neutrophilia.

Fig. 7.—Hyperplastic bone-marrow, showing the decrease in number of fat spaces and the great excess of cellular tissue. The specimen was taken from a case of tuberculosis of the knee with secondary infection; leucocytosis had been observed for three months (× 90).

The subsidence of an infection, and the period of convalescence are associated with changes of extreme importance. The neutrophiles gradually fall to normal numbers, but the lymphocytes increase, both relatively and absolutely, to figures well above normal (post-infective lymphocytosis). The eosinophiles and often the monocytes also show an increase during convalescence. These post-infective cytoses may be most confusing if no history of the case is available.

Hickling has shown that these "post-infective" phenomena occur after the production of sterile abscesses, and, therefore, do not represent any part of the response to infection. It may well be supposed that they are changes concerned with repair rather than with direct reaction.

2. **Increased Functional Demand as a Cause of Neutrophilic Leucopenia (Neutropenia).**—Infections similar in kind to

those discussed above, but much more intense may be accompanied by a reduction in the number of leucocytes. Changes, in the form of a shift to the left of the neutrophiles, are invariable, even in these cases. A very large percentage of the cells show degenerative changes, which are attributable to injury while in the bone marrow rather than when in the circulation. Occasionally the neutrophiles, practically without exception, may possess band-like nuclei. In such cases there are few or no very young metamyelocytes in the circulation or in the marrow ; presumably some toxic agency has caused a complete alteration in the process of maturation of the neutrophilic cells, and, as might be expected, the prognosis in such cases is extremely grave.

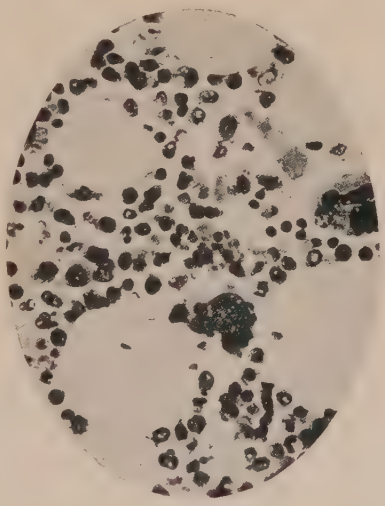

FIG. 8. — Hyperplastic bone-marrow, showing a part of the tissue seen in Fig. 7 at a higher magnification. The characters of the proliferated cells are better seen, and the participation of even the megakaryocytes is obvious (× 225).

Excessive demand upon the resources of the marrow need not necessarily be an acute process associated with more or less sudden failure of myeloid function ; it may occur in long-continued infections as the result of a persistent drain. The failure to produce the requisite number and quality of cells is here a gradual one, and is associated with a peculiar form of " gelatinous " degeneration of the hyperplastic marrow. Fig. 11 shows the appearances of this condition, and should be compared with

Fig. 7, in which simple hyperplasia of myeloid tissue is shown.

Gelatinous degeneration of the marrow can occur in the complete absence of infection; it is not uncommon in diseases producing a severe cachexia, and can be caused experimentally by deficient diets. Presumably, in chronic infections, the marrow receives too little of some essential foodstuff required for cytopoiesis, and, therefore, degenerates.

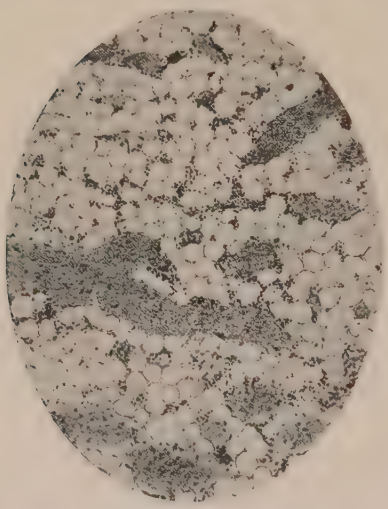

Fig. 9.—Depletion of bone-marrow showing almost complete absence of cells, with no signs of regeneration. The case was one of pneumonia following perforation of a gastric ulcer (× 90).

3. Increased Functional Demand as a Cause of Lymphocytosis.—It has been mentioned above that lymphocytosis occurs in the post-infective stages of many maladies as a sign of the onset and progress of reparative processes; it is, therefore, an indication of an infective lesion, which has been overcome or, at least, is being held in check. Lymphocytosis is not strictly an indication of chronicity of an infection, although it accompanies most chronic infective processes, which are, after all, infections held in check. This interpretation of lymphocytosis as an indirect reaction does not fit all cases, but is well illustrated by typhoid fever. In this disease lymphocytosis, relative or absolute, is the rule. It disappears and is replaced by neutrophilia only in cases with a very bad prognosis. In other words, the disap-

pearance of the lymphocytosis indicative of an efficient holding in check of the infection is an evil sign. It is thus clear that

4. **Increased Functional Demand can be a cause of Lymphocytopenia.**—This is almost invariably of bad significance. It is well to realise that any form of leucocytosis is not a condition essentially different from leucopenia. The two conditions differ only quantitatively, and are not necessarily of different origins.

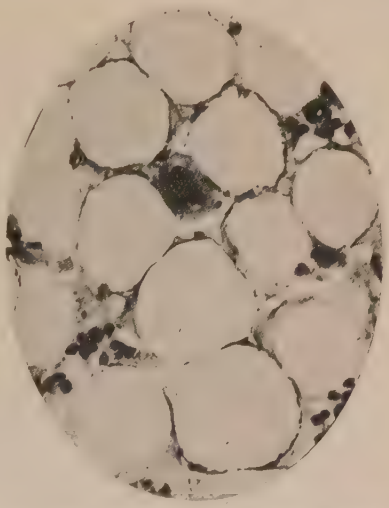

FIG. 10.—Depleted and injured bone-marrow, showing a part of the tissue seen in Fig. 9, at a higher magnification. The pyknosis of the nuclei is clearly seen (× 225).

5. **Increased Functional Demand as a cause of Eosinopenia** is a common condition and occurs in an indirect manner. Such infections as that of scarlatina, which are normally associated with neutrophilia and eosinophilia, show eosinopenia when the infection is very severe and the neutrophilia very extreme. Here it is possible that the eosinopenia results from overstimulation of the formative cells, but it is more probably due to the great activity of production of neutrophiles, *i.e.*, it is a phenomenon similar to the eosinopenia occurring in ordinary infections, as previously described.

6. **Increased Functional Demand as a cause of Eosinophilia.**—The functions of the eosinophilic granular leucocytes are not understood, and, therefore, it is never possible to be certain that an increase in their number in the circulation is

due to a direct functional demand. It is known that many infestations with metazoan parasites are associated with eosinophilia, but the relationship of the two conditions is not clear. Neutrophilia is usually in the nature of a protective response, but it is doubtful whether this is the case with eosinophilia, which is a much less stable condition. The eosinophilia associated with hydatid disease disappears

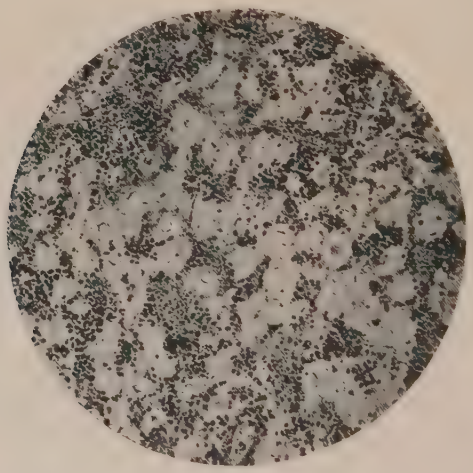

Fig. 11.—Gelatinous degeneration of bone-marrow, showing the decrease in the number of cells, together with deposition of structureless material in the interstices of the tissue. The tissue is from a case of persistent suppuration of a tuberculous knee-joint which had lasted several years (× 90).

if suppuration of the cyst occurs ; it seems that neutrophilia, which is the response of the body to the more lethal condition, is a more mobile reaction.

Post-infective eosinophilia has already been mentioned, and it is difficult to imagine that it occurs as a response to an increased functional demand, although it is equally difficult to imagine any other cause.

7. **Decreased Hæmatopoietic Function as the result of Destruction of Formative Tissues** occurs both in widespread

injuries of lymphatic and of myeloid tissues. Extreme degrees of lymphocytopenia may accompany extensive destruction of lymphatic tissue by widespread tuberculosis, or, much more rarely, by malignant tumours.

Great decrease of myelopoiesis may occur in the last stages of cases with extensive metastatic tumours in the bone marrow, as a result of simple destruction of the myeloid tissue by the infiltrating neoplasm.

The greatest general decrease of hæmatopoiesis is, of course, that occurring in aplastic anæmia (p. 164).

8. **Increased Functional Activity as a result of Greater Size of the Formative Tissues.**—The most obvious example of this is found in the leucoses, where, so far as is known, there is no increased functional demand. The leucocytosis appears to be the result entirely of the myeloid hyperplasia. Some forms of polycythæmia (p. 145) seem to arise in a similar manner.

Excess of lymphatic tissue in the body in status lymphaticus can result in a well-marked lymphocytosis, due to the increased bulk of the formative tissue, and not to an altered functional requirement of the body as a whole. Lymphatic hyperplasias, such as occur in association with some endocrine disorders, particularly exophthalmic goitre, are accompanied by lymphocytosis of similar origin.

Some *examples* of the application of the general principles so far enunciated may now be convenient. In each case the blood picture will be described in the terms introduced by Victor Schilling.

It is obvious that a much better insight into the progress of leucocytic changes due to infection will be obtained from a series of observations rather than from a single examination, and the first cases here cited were investigated in this way. The preparation of a chart similar to a temperature chart to illustrate the results obtained is always an advantage ; this plan is followed here. Two types of chart can be made : the one shows the percentages of neutrophiles

in the blood, the percentage of mature and of immature neutrophiles as separate lines. The second type of chart, which is only supplementary to the first, shows rather finer details, in that it is prepared to demonstrate the percentage of immature neutrophiles, of band forms and of young forms as separate curves. Although the second type of chart gives a deeper insight into the processes at work, the first variety will serve for most purposes. Fig. 12 shows the

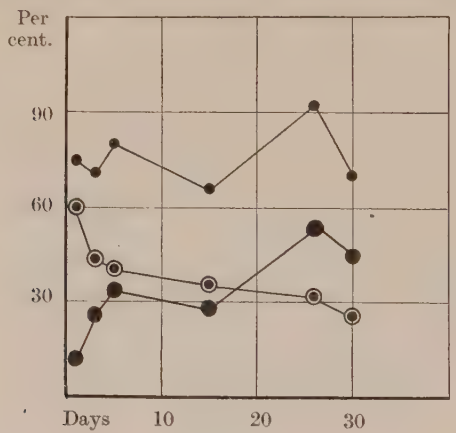

Fig. 12.— = Total neutrophils.
= Mature neutrophils.
= Immature neutrophils.

leucocytic changes occurring in a case of suppuration of the knee joint. The percentage of neutrophiles varied a little at different times during the illness, but the alterations bore no relationship to the clinical phenomena. It is clear that the mature neutrophiles (polymorphonuclears) fell steadily, while the immature forms (young metamyelocytes and metamyelocytes with band nuclei) rose almost equally regularly until the fatal termination of the malady. Fig. 13 is an amplification of Fig. 12, and shows the more detailed appearances, by separation, on the chart, of the two forms

of metamyelocyte from one another. At the end of the disease there were almost as many young forms as band forms in the circulation.

The hæmatological findings do not always correspond

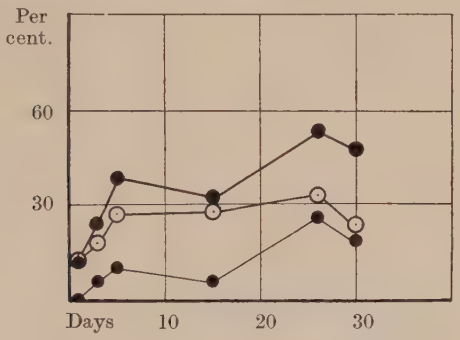

FIG. 13.— ●——● = Total immature leucocytes.
⊙——⊙ = Band forms.
●——● = Young forms.

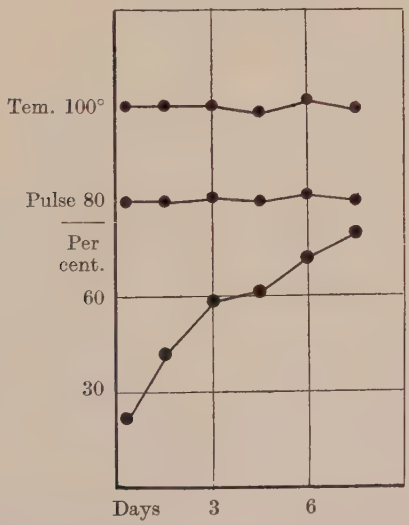

FIG. 14.—The rising percentage of immature cells (lowest curve) is clearly seen.

with the clinical phenomena. This is shown in Fig. 14, which demonstrates the pulse, temperature and blood picture of a case of peritonitis. In spite of a persistent rise of immature neutrophiles, the temperature and pulse showed no variation even up to the time of death. Clearly, in such a case, the examination of the blood gives the clearest insight into the condition of the patient.

During recovery from an infection the appearances naturally are the reverse of those so far described. Fig. 15

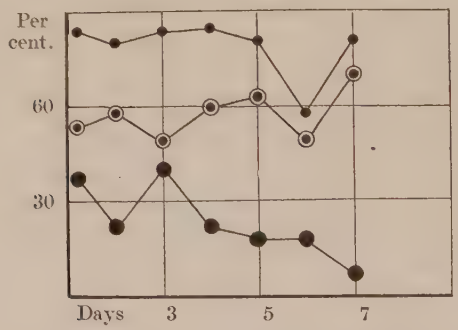

Fig. 15.— = Total neutrophiles.
= Mature neutrophiles.
= Immature neutrophiles.

shows the gradual reduction of immature neutrophiles to normal numbers in a case of erysipelas, although the total percentage of neutrophiles varied very little during the disease.

For most clinical purposes it is unfortunately not possible to obtain graphic results of serial examinations, and only one investigation is, as a rule, available for interpretation. It is commonly possible to draw some valuable conclusions even from the result of a single observation.

The findings in a well-marked case of suppuration will serve to make clear the condition of affairs. In a case

of suppuration in the pelvis, the blood picture was as follows :—

Leucocytes	20,000 per c.mm.	
Eosinophiles	*Nil.*	
Basophiles	*Nil.*	
Lymphocytes	5 per cent.	
Monocytes	1 ,,	
Myelocytes	*Nil.*	Total neutrophiles, 94 per cent.
Young forms	19 per cent.	
Band forms	14 ,,	
Polymorphs	61 ,,	

Here there is well-marked leucocytosis and a great neutrophilia with absence of eosinophiles. This alone would indicate the presence of infection, but, when the large number of young and band forms of neutrophiles are taken into account, there can be no doubt of the diagnosis.

Even the mildest of infective conditions can cause alterations in the blood picture ; this is well seen in a case of mild catarrhal inflammation of the appendix, which showed signs of an older lesion in the form of fibrosis. The symptoms were confined to slight discomfort in the right iliac fossa. The blood showed :—

Leucocytes	8,000 per c.mm.	
Eosinophiles	1 per cent.	
Basophiles	*Nil.*	
Lymphocytes	16 per cent.	
Monocytes	8 ,,	
Myelocytes	*Nil.*	Total neutrophiles, 75 per cent.
Young forms	*Nil.*	
Band forms	12 per cent.	
Polymorphs	63 ,,	

Here the number of leucocytes is at the high limits of normal, but there is no definite leucocytosis ; the neutrophilia is very slight, and the eosinophiles are but little reduced. The main difference of the picture from normal lies in the presence of 12 per cent. of band form neutrophiles,

i.e., there is a slight shift to the left. Taken together with the clinical history, there could be no doubt as to the diagnosis of a mild infection.

The interpretation of a difficult case may be helpful. A mentally defective man complained of pain in the right iliac region, where a scar was present, about the origin of which he could give no coherent information. The blood showed :—

Leucocytes	7,500 per c.mm.	
Eosinophiles	1 per cent.	
Basophiles	*Nil.*	
Lymphocytes	49 per cent.	
Monocytes	2 „	
Myelocytes	*Nil.*	Total neutrophiles, 48 per cent.
Young forms	*Nil.*	
Band forms	1 per cent.	
Polymorphs	47 „	

The feature of this blood picture is the presence of lymphocytosis not associated with total leucocytosis or shift to the left of the neutrophiles. There is, however, some reduction in number of the eosinophiles, which is so common an accompaniment of infections. Lymphocytosis has already been stated to be usual in chronic infections, and eosinopenia is very characteristic of all infective conditions. It seemed certain that, in this case, some mild and scarcely progressive infection must be present, and operation revealed adhesions around the cæcum and absence of the appendix.

One case may be quoted to show that the method may give results of great clinical value, quite apart from their theoretical interest. A man with Jacksonian epilepsy showed a scar on the scalp, which was stated to be the result of an injury received some eight months previously. The attacks were attributed to a cicatrix on the cortex. Blood examination showed a condition definitely indicative of the presence of an infection ; it could, of course, not be localised simply on the results of a blood examination, but

operation revealed the existence of a cerebral abscess. The blood had shown :—

Leucocytes	6,000 per c.mm.	
Eosinophiles	1 per cent.	
Basophiles	*Nil.*	
Lymphocytes	8 per cent.	
Monocytes	12 ,,	
Myelocytes	*Nil.*	Total neutrophiles, 79 per cent.
Young forms	8 per cent.	
Band forms	33 ,,	
Polymorphs	38 ,,	

The characters are those already described as indicative of infection.

Prognostic, as well as diagnostic, indications, can often be obtained from a differential blood count of this type, but usually serial examinations are necessary. A single observation may occasionally suffice, particularly in cases of a severe character. A man on whom appendicectomy had been performed about eight months before the onset of his present illness was seized by a severe febrile malady, which had the characters of septicæmia. His blood showed :—

Leucocytes	15,000 per c.mm.	
Eosinophiles	*Nil.*	
Basophiles	*Nil.*	
Lymphocytes	7 per cent.	
Monocytes	4 ,,	
Myelocytes	*Nil.*	Total neutrophiles, 89 per cent.
Young forms	43 per cent.	
Band forms	40 ,,	
Polymorphs	6 ,,	

The neutrophiles showed the " toxic " changes, which, of course, occur in all infections, in the most extreme degree, and the number of mature forms was almost negligible. There could be no doubt that a person with so extreme a shift to the left could not possibly recover. A further clinical diagnosis of sub-phrenic abscess was made, and, as the patient's clinical condition, although grave, did not appear as hopeless as did the blood picture, operation was

attempted. A sub-phrenic abscess was found and dealt with. For three or four days the patient appeared to be recovering, but then gradually failed, and died on the tenth day with the following blood picture :—

Leucocytes	3,600 per c.mm.	
Eosinophiles	*Nil.*	
Basophiles	*Nil.*	
Lymphocytes	2 per cent.	
Monocytes	5 ,,	
Myelocytes	*Nil.*	Total neutrophiles, 93 per cent.
Young forms	61 per cent.	
Band forms	30 ,,	
Polymorphs	2 ,,	

It is, of course, not possible to formulate rigid *indications of prognosis*, but certain suggestions may be of value :—

1. A slight degree of neutrophilia with distinct nuclear shift and persistence in the circulation of eosinophiles may be a physiological condition. In the later stages of pregnancy changes of this type may occur with, of course, no " toxic " alterations in the neutrophiles. A relative reduction of eosinophiles without any notable alteration in the number of these cells per cubic millimetre of blood is quite common.

A multipara, in the seventh month of pregnancy, showed :—

Leucocytes	7,600 per c.mm.		
Eosinophiles	3 per cent.	= 228 per c.mm.	
Basophiles	1 ,,	= 76 ,,	
Lymphocytes	16 ,,	= 1,250 ,,	
Monocytes	3 ,,	= 228 ,,	
Myelocytes	*Nil.*	Total neutrophiles, 77 per cent. = 5,852 per c.mm.	
Young forms	3 per cent.		
Band forms	11 ,,		
Polymorphs	63 ,,		

Toxic changes are, of course, always absent.

A blood picture similar to that described above may occur in mild infections, and, if it does not deteriorate, is of excellent prognostic significance.

2. Slight or definite leucocytosis with nuclear shift of moderate degree (not more than 4 per cent. of young forms, and 12 per cent. of band forms), decrease of eosinophiles and slight diminution of lymphocytes comprises a picture from which no clear prognostic inferences can be drawn. It is, however, indicative of the need of further examinations at short intervals ; but there could be no doubt as to the existence of an infection.

3. High leucocytosis with great shift to the left, tending to progress in the same direction, with great decrease or even disappearance of eosinophiles and reduction of lymphocytes is a grave condition, which may, however, still be recoverable. It is particularly in cases in which the percentage of young forms exceeds that of band forms that the outlook is very grave.

4. The persistence of a progressive fall of the total number of leucocytes, with an extreme and increasing shift to the left, total absence of eosinophiles, and well marked lymphopenia are characteristics of moribund cases. It may be stated, as a general rule, that progressive eosinopenia with rising leucocytosis is indicative of progressing infection to which some reaction is occurring, whereas progressive eosinopenia with a falling leucocyte count indicates the presence of an infection, which has overpowered the defensive mechanisms.

5. Re-appearance of eosinophiles and fall of neutrophiles in cases in which the former have been absent and the latter excessive is indicative of recovery, and is always accompanied by a progressive movement of the nuclear index towards normal.

6. The development of lymphocytopenia during the course of persistent infections is always of bad significance.

7. A sudden fall of the number of lymphocytes in association with progressive neutrophilia always indicates an extension of the inflammatory process ; the prognosis is definitely bad in those cases in which lymphocytopenia occurs during a

time of progressive decrease of the total leucocytes and shift of the neutrophiles to the left.

8. Lymphocytosis following neutrophilia and accompanied by eosinophilia with progressive passage of neutrophiles towards normal, both in number and " index," is indicative of recovery or even of convalescence.

The cases so far described illustrate infective " leukæmoid " reactions of which the main character is an alteration in the neutrophilic leucocytes. There are, in addition, cases in which the most notable change affects other cell-types, although it is probable that in all of them there is some alteration of the neutrophiles also.

Leukæmoid blood pictures in which some form of cell other than the neutrophile predominates in the blood usually show appearances indicative of less intensity of reaction than do the more usual cases with their pronounced alterations of the neutrophiles in both number and quality. The term leukæmoid reaction is here being used to designate any blood picture in which there is increase in the number of immature cells in the circulation, but it does not apply to simple excess of one cell-type without appearance, in the circulation, of less differentiated cells.

A slight degree of lymphatic leukæmoid reaction is seen in many cases of endocrine disturbance. This is usually most obvious in exophthalmic goitre, which is, as is well known, associated with general hyperplasia of lymphatic tissue, particularly in the thymus. The following is a characteristic blood picture in this disease :—

Leucocytes	6,300 per c.mm.	
Eosinophiles	5 per cent.	
Basophiles	*Nil.*	
Lymphocytes	38 per cent.	
Monocytes	8 ,,	
Myelocytes	*Nil.*	Total neutrophiles, 49 per cent.
Young forms	1 per cent.	
Band forms	3 ,,	
Polymorphs	45 ,,	

The features of this record are: Slight, but definite, lymphocytosis, eosinophiles at the upper limits of normal, and shift to the left of the neutrophiles. The alteration of the neutrophiles is quite unlike that seen in the infections previously described, in which the number of band forms is always greatly in excess of the normal 4 per cent. at the time of appearance of the young forms. Here we see a picture which seems to indicate a simple defect of the regulation of emigration. Ordinary infections associated with shift to the left of the neutrophiles are not accompanied by a high percentage of eosinophiles. These are numerous only in one form of infection, viz., scarlet fever, which is, however, characterised by high leucocytosis, which is absent in exophthalmic goitre. In any case, the lymphocytosis of this latter disease distinguishes it from the ordinary infections. Eosinophilia of mild degree is usual in disorders of internal secretory function, and monocytosis up to about 15 per cent. is not rare.

Post-infective eosinophilia is associated with nuclear shift of the neutrophiles, and can, therefore, be regarded as being a leukæmoid blood change. The eosinophilia accompanying helminthic infestations is an isolated phenomenon in the blood without any concurrent changes in the neutrophiles, and so does not fall into the group of leukæmoid reactions.

One of the most interesting leukæmoid changes is that accompanying *glandular fever* in which the blood shows a well-marked monocytosis in addition to a considerable degree of nuclear shift of the neutrophiles. Owing to the benign character of this " infective mononucleosis," nothing is known of the underlying pathological changes.

The leukæmoid reactions and blood pictures are of considerable clinical importance, and more intelligent reasoning can be applied to them if their character is recognised than if they are dismissed as being simple leucocytoses. Information as to the genesis of leukæmoid blood pictures (including

leucocytosis in the ordinary sense) is scanty, but some indications of the line of thought can be presented.

The normal number of leucocytes in the circulation is not subject to any great persistent variation; digestion or muscular exercise may cause a temporary alteration, but this is only transient. There is, of course, a considerable and perpetual destruction of leucocytes in various parts of the body, and particularly in the spleen, which seems to be the organ in which aged white cells meet their end. This continual removal of leucocytes from the circulation is made good by further production of these cells in the formative tissues, and it is obvious that the two processes are inter-related and approximately balanced. Arneth contends that the alterations in the number of circulating leucocytes in pathological conditions is the result of the same processes, altered by excessive destruction and production. Leucocytosis would, on this hypothesis, result from increased formation accompanied by an excessive destruction of a less degree of intensity than the production. There would naturally be a shift to the left (*i.e.*, an increasing immaturity) of the cells leaving the hæmatopoietic tissues, and Arneth claims that all the other forms of leucocytes also manifest immaturity in the character of their nuclei. Peripheral destruction of much greater intensity than leucocyte production would cause leucopenia, which would also show well-marked nuclear shift. This would tend to be progressive on account of the ever-greater attempt of the marrow to produce a sufficient number of cells to replace those destroyed. Some infective states show a normal number of leucocytes, but extreme nuclear shift; these presumably represent a condition in which destruction and formation, at a much greater rate and intensity than normal, are practically balanced processes.

There is little doubt that Arneth's view corresponds with the conditions found in most cases, but there are certainly some exceptions. The leucocytosis of leukæmia and that

seen in moribund persons do not depend upon any increase of peripheral destruction, and the same applies to cases of metastatic tumours of bone marrow. Further, there are infective cases also in which Arneth's conception is almost certainly incorrect. Infections which, when not excessively virulent, stimulate the myeloid tissue, can, in greater concentration, inhibit its function, absolutely or completely. Some infective cases, in which there is a normal or even a reduced number of leucocytes, show an astonishing percentage of immature neutrophiles; this appearance might be supposed to be due to emigration of incompletely formed normal cells from the bone marrow. This view does not, however, correspond with observed facts. The marrow in these cases shows a far greater number of myeloblasts than is seen in normal extra-uterine life, and the majority of the granular cells present are immature neutrophiles. One gains the impression that the normal process of formation of mature neutrophiles by ripening of the daughter cells of myelocytes has been superseded by a more embryonic type of process in which the neutrophiles are derived from the myeloblast. Inhibition of full maturation of the cells has occurred at a stage earlier than that of real segmentation, probably because the developmental cycle has been lengthened by production of neutrophiles from a less mature type of cell than normally. This would account for the predominance of the band type of the nucleus in the neutrophiles in these circumstances, *i.e.*, the development of neutrophiles has started one stage earlier than normal, and also ends in a condition just one degree short of segmentation. It might be well, in the light of these facts, to refer to *metaplastic shift to the left of the nuclear index* in these cases.

Equally, it is appropriate to refer to the cases of inhibited marrow function and consequent shift to the left as being degenerative in type. These statements would imply that a leucocytosis might depend almost entirely upon the activity of a degenerate marrow. Figs. 16 and 17

show that this can really be the case, and the blood may then contain only immature leucocytes.

These degenerative changes doubtless indicate a stage in the development of a more complete aplasia of the myeloid tissue, such as is shown in Fig. 16. This specimen came from a case of prolonged suppuration in which an extreme leucocytosis was gradually replaced by an equally extreme degree of leucopenia. Almost the only type of

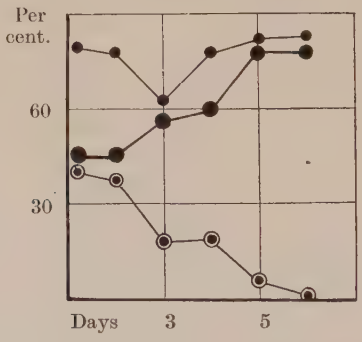

Fig. 16.— = Total neutrophiles.
= Mature neutrophiles.
= Immature neutrophiles.

cell (and this was scanty) left in the marrow was the normoblast.

Infective leucocytoses can thus not be regarded as being invariably the result of alteration of balance of two processes, normal in every respect except intensity of function.

The present chapter can conveniently contain an account of certain anomalous responses of the hæmatopoietic tissues to infection; these can all be included in the term "lymphatic reaction," as suggested by Türk.

It has already been mentioned that certain very intense infections are accompanied by severe neutropenia and absolute or relative lymphocytosis. I have seen a case of peritonitis with a total leucocyte count of 900 per cubic millimetre,

and 780 of the cells were lymphocytes. Türk seems to have been among the first to observe cases of this description, and regards them as resulting from the interaction of two factors, viz., a peculiar type of infection and an atypical hæmatopoietic system. In some cases the blood picture is almost that of aleukæmic lymphadenosis. Jagic and Schiffner recorded a case with 2,400 leucocytes per cubic millimetre of blood, and 74 per cent. of these were lympho-

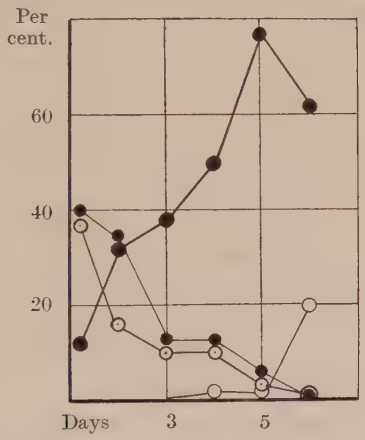

Fig. 17.— = Young forms.
= Band forms.
= Mature neutrophils.
= Myelocytes.

cytes. The process at work in these lymphatic reactions is, however, essentially different from that of leucosis, as is shown also by the fact that a few cases of recovery are on record. The fact that diseases accompanied by such blood pictures are not always fatal suggests also that some constitutional peculiarity is present, and that the reaction does not depend entirely upon the nature of the infective agent.

There is definite disturbance of the whole hæmatopoietic mechanism in some cases, as was shown in one described

by Reiche in which acute sepsis was accompanied by leucopenia with a lymphatic reaction, purpura and reduction in the number of platelets.

The view of Jagic and Schiffner, and Türk, that the essential nature of these conditions is to be sought in constitutional disposition is opposed by Naegeli, who believes rather that a special infective agent is at work, and manifests itself by stimulation of lymphatic tissue. The latter view seems to have much to support it because it is known that the neutrophilia of most infections is in the nature of a defensive mechanism. It is possible to understand how a very severe infection could completely paralyse this mode of reaction, but it is less clear how it could cause stimulation of lymphatic tissue, which produces cells of no known value in neutralising the effects of most bacteria. As Marchand points out, that one could agree with the possible existence of a constitutionally defective granulocytic system, but its presence would not explain the lymphocytosis. Further, the fact that certain cases with extreme monocytic reactions (see later) occur also seems to suggest a special infective agent rather than a special constitution.

The term *agranulocytic angina* (Friedemann) or simply *agranulocytosis* (Werner Schultz) has been applied to a disease occurring most frequently in middle-aged women, and characterised by fever, severe ulcerative and gangrenous processes in the mouth and pharynx, and a peculiar blood picture. There is extreme leucopenia and almost total disappearance of granulocytes from the blood, which contains, therefore, only red corpuscles, lymphocytes and monocytes. The effect of the infection is shown almost entirely in the diminution of the neutrophiles, but eosinophiles and even platelets are, as a rule, unaffected (Friedemann). There is thus no complete aplasia of the myeloid tissue. David found myeloblasts and eosinophilic myelocytes and polymorphonuclear cells in the marrow, although neutrophiles were absent. The fact that the defect is one of regulation of cell

emigration only probably accounts for the complete absence of myeloid metaplasia in the body.

There is more variation in the incidence of the disease than was thought by the first writers on the subject. Thus Ehrmann and Preuss describe it in males, and Bantz has seen it in a boy, aged four ; Lauter has even seen recovery in one case.

The fact that recovery is not impossible suggests that agranulocytic angina is only a form of the much less severe monocytic angina described by W. Schulz in which monocytes may number anything up to 80 per cent. of the total leucocytes. Even this disease represents a more severe form of a similar malady in which no pharyngeal changes occur but the blood picture is similar in character (Kwasniewski, Henning). It is possible that " glandular fever " is only another type of the same disease.

The available evidence seems to support the idea of a special infective agent, and it seems reasonable to agree with Elkeles that the cases in which sepsis is a prominent feature are only secondarily complicated. All these contentions seem to suggest that agranulocytosis should be regarded as a special morbid entity, but there are objections to such a position. Any one of the characteristic features of the malady, such as absence of purpura, normal number of platelets, absence of splenomegaly, and normal number of red corpuscles may not be present. These facts have led Jagic and Schiffner to conclude that lymphatic reaction represents the response of predisposed persons to infections of relatively little intensity, while lymphatic leukæmia would represent their mode of reaction to more severe sepsis. In investigations of status lymphaticus some evidence has been adduced that acute leukæmia does occur most commonly in constitutionally peculiar persons, but that alone is insufficient ground for considering it to be of infective origin. Zadek is prepared to agree that agranulocytosis is not a disease *sui generis*, but will not admit the

importance of a constitutional anomaly, because, as he very rightly remarks, the blood, in cases of recovery from the disease, returns completely to normal conditions.

The fact that monocytes form so large a part of the response in some of these cases would suggest that, if the disease is really an ætiological entity, these cells have a special formative system of their own. This view has been controverted earlier in this book, although it is vigorously supported by Schilling.

It is not possible to do more than conclude that agranulocytosis is a special mode of reaction to infection, but the cause of the hæmatological peculiarities is quite unknown.

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Figs. 7 to 17 reprinted from the *Brit. Journ. of Surgery*, 1926, xiv., pp. 9–35.

CHAPTER VI

LEUKÆMOID REACTIONS

II. Non-infective

The only non-infective form of leukæmoid reaction of importance is that seen accompanying the presence of lymphadenoma or of secondary deposits of malignant tumours in the bone marrow; the latter have already been mentioned, but are given fuller consideration in the present chapter.

The formation of secondary deposits can occur as the result either of permeation of lymphatic channels or of the lodgement of emboli deposited from the blood stream. The invasion of the bone marrow occurs by deposition and growth of emboli brought in the blood stream; this is shown by the absence of lymphatic channels from the marrow, and also by the fact that such metastases are found first in the interior of the medullary cavity, *i.e.*, they do not reach it by erosion of the compact bone from without inwards.

The very great majority of secondary neoplastic deposits in the long bones occur either at the junction of the upper third with the lower two-thirds of the humerus or in a similar position in the femur; extension of the process in the distal direction is quite common, but the first site of involvement is the place mentioned. There is an anatomical peculiarity which probably explains this site of predilection. In the normal adult, red marrow is confined to a small area at the upper ends of the humeri and femora, in addition, of course, to the larger hæmatopoietic depôts in the vertebral column and ribs. The vascular arrangement of fatty and cellular or red marrow are very different; in the former the blood

vessels are quite ordinary in structure, but when the junction with the red marrow is reached a considerable change occurs. The red marrow, as compared with the fatty, is a very vascular tissue, but all its vessels are derived from those present in the adjacent adipose tissue. Such increase of vascularity can occur only by the breaking up of the larger trunks present in the fat into small blood channels in the formative marrow; this is, in fact, what does occur. The vessels in the myeloid tissue proper are reduced to channels lined by a single layer of "endothelium," which has already been described as being hæmatopoietic. The sudden widening of the bed of the stream at the junction of the two types of marrow must be associated with a great slowing of the rate of flow. It is already known that erythroblasts can divide and mature inside the vessels of the marrow, and it is not difficult to understand the impaction and continued growth of tumour cells caught in such a tissue.

Practically any type of neoplasm may give rise to metastases in bone marrow, but of course such growths as epithelioma, which are not prone to general dissemination, rarely invade bone. It is usually a hard carcinoma of chronic course that gives off the necessary emboli, rather than a more cellular and rapidly growing mass; this may perhaps be due to obliteration of lymphatic channels by the process of peri-lymphatic fibrosis, as described by Handley, in the former case, with consequent spread of the tumour cells into blood vessels. Any type of sarcoma may give rise to deposits in the marrow, as might well be expected in the case of these tumours, which always tend to produce metastases *viâ* the blood stream.

The intra-vascular position of the emboli in the blood channels of the marrow almost immediately causes grave alteration of the erythropoietic process; spread of the growth into the surrounding marrow tissue causes equally severe interference with leucocyte formation.

There are two main types of blood change associated with

metastatic tumours of the marrow; the one simulates pernicious anæmia to some extent, while the other is more definitely leukæmoid.

The case recorded by Harrington and Teacher is an excellent illustration of the first variety of blood change; the blood picture showed :—

Red corpuscles	1,600,000 per c.mm.
Hæmoglobin	35 per cent.
Colour index	1·09
Leucocytes	14,000 per c.mm.
Polymorphs	63·0 per cent.
Eosinophiles	0·7 ,,
Lymphocytes	16·7 ,,
Monocytes	18·8 ,,
Myelocytes	0·8 ,,

Myeloblasts in unspecified number were also present.

In counting 500 leucocytes, 29 large and 4 small nucleated red cells were seen, *i.e.*, 924 per cubic millimetre of blood.

Really the only resemblance to pernicious anæmia lies in the rise of colour index above unity; the leucocytosis and the neutrophilia are quite incompatible with such a diagnosis.

Bizzarri has recorded a very striking example of the leukæmoid type of blood picture in a case in which the primary growth was in the stomach :—

Red corpuscles	1,200,000 per c.mm.
Hæmoglobin	15 (Fleischi)
Colour index	0·62
Leucocytes	13,300 per c.mm.
Polymorphs and metamyelocytes	41 per cent.
Eosinophiles	1 ,,
Lymphocytes	20 ,,
Monocytes	6 ,,
Myelocytes	7 ,,
Premyelocytes	9 ,,
Myeloblasts	13 ,,

There were, in addition, 24,700 nucleated red cells per cubic millimetre of blood.

I have recorded a case in which similar blood changes

occurred in association with marrow metastases derived from a primary carcinoma of the stomach, but the number of nucleated red cells was even higher than in Bizzarri's case :—

Red corpuscles	1,200,000 per c.mm.
Hæmoglobin	15 per cent.
Colour index	0·6
Leucocytes	30,000 per c.mm.
Polymorphs	47·5 per cent.
Metamyelocytes	12·0 ,,
Myelocytes	12·5 ,,
Myeloblasts	5·0 ,,
Lymphocytes	21·5 ,,
Monocytes	1·5 ,,

Stained films showed poikilocytosis, anisocytosis and polychromasia, but the most striking feature was the presence of very large numbers of nucleated red cells ; while counting 1,000 leucocytes in stained films, 2,830 erythroblasts were seen ; this, of course, represents nearly 85,000 per cubic millimetre of blood. More than 29,000 of these cells were macro-normoblasts, leaving over 55,000 of the ordinary small type.

There are cases in which the blood changes are very much less intense, and are not accompanied by leucocytosis ; even reduction in the number of red corpuscles is not an essential feature. A case in which secondary deposits of spindle-celled sarcoma invaded many bones of the skeleton makes clear this condition :—

Red corpuscles	5,984,000 per c.mm.
Hæmoglobin	78 per cent.
Colour index	0·65
Leucocytes	8,600 per c.mm.
Eosinophiles	1·0 per cent.
Lymphocytes	7·4 ,,
Monocytes	5·0 ,,
Polymorphs	77·0 ,,
Metamyelocytes	3·0 ,,
Myelocytes	6·0 ,,
Myeloblasts	0·6 ,,

In this case there were only about 35 normoblasts per cubic millimetre.

It must not be supposed that the differences between the last mentioned case and the previous ones depend upon the sarcomatous character of the neoplasm ; Dieballa and Entz have described a case of metastasis in bones derived from a spindle-celled sarcoma, primary in the pleura in which the blood changes were very similar to those already described, viz. :—

Red corpuscles	2,608,000 per c.mm.
Hæmoglobin	41 per cent.
Colour index	0·78
Leucocytes	112,600 per c.mm.
Polymorphs	82·8 per cent.
Eosinophiles	0·7 ,,
Basophiles	0·2 ,,
Monocytes	2·3 ,,
Lymphocytes	3·6 ,,
Neutrophilic myelocytes	9·8 ,,
Eosinophilic myelocytes	0·25 ,,
Myeloblasts	0·1 ,,

There were here only 300 normoblasts per cubic millimetre.

A number of interesting points arise in the discussion of the blood changes and the underlying causes of their appearance.

It has already been contended that secondary deposits of malignant tumours in bone marrow occur as the result of the lodgement of emboli composed of tumour cells ; these reach the marrow by way of the blood stream. There can be no doubt about this statement in the case of sarcomata, and even carcinoma cells can be demonstrated in the lumen of blood vessels (Plate IV., Fig. 37) ; the method of formation of lymphadenomatous nodules in the marrow and their effects on the blood are discussed in Chapter VII., but here it can be stated that the blood picture is the same as that of secondary carcinosis of the marrow.

The emboli lodge in the red marrow rather than in the

fatty tissue, because the increased vascularity and consequent slower flow of blood permits of their effective colonisation and subsequent growth. That proliferation of cells can occur in the vessels of the formative marrow is shown by the normal occurrence of erythropoiesis in this position.

The presence and growth of the metastases are definitely irritative to the surrounding myeloid tissue, which becomes hyperplastic; and further secondary deposits can, and often do occur in the newly-formed hæmatopoietic marrow.

It is only to be expected that the impaction and growth of tumour cells in the marrow vessels will interfere with the formation of red cells; this is shown by the appearance of erythroblasts in the circulation. There must also be injury to the histiocytic lining of the marrow vessels which will interfere with leucopoiesis, as will also the continued growth of the neoplastic cells as they infiltrate the rest of the tissue; this is shown by the appearance of immature myeloid cells in the circulation.

There is, thus, more than a simple mechanical disturbance of the formative tissue by the growth; there is definitely a reaction on the part of the marrow cells. This will naturally vary in intensity in different cases, and a variety of blood pictures will result. The only resemblance to the blood picture of pernicious anæmia lies in the occasional occurrence of a colour index just above unity, but the absence of megalocytes and megaloblasts, both from the blood and the formative organs, completely obviates mistake.

A tabular differentiation may be of use :—

Carcinosis of the Marrow	Pernicious Anæmia
1. Reduction in number of red corpuscles, except in rare cases.	Reduction in number of red corpuscles, except in very early stages, and sometimes in remissions.
2. Colour index usually below unity, but rarely above.	Colour index usually above, but sometimes unity.

Carcinosis of the Marrow—*contd.*	**Pernicious Anæmia**—*contd.*
3. Anisocytosis due to presence of macro-normocytes and other atypical corpuscles.	Anisocytosis due to presence of megalocytes and other atypical corpuscles.
4. Erythroblasts in small or large numbers (macro-normoblasts and normoblasts).	Megaloblasts present in small numbers, and normoblasts only in definitely anæmic stages.
5. Most commonly leucocytosis, less often normal number or leucopenia.	Leucopenia.
6. Excess of myeloid leucocytes.	Relative lymphocytosis.
7. Immature myeloid leucocytes always present, but in varying numbers.	Immature myeloid leucocytes not invariable, and always scanty.

The characteristic changes in the blood picture do not occur in every case; this might be expected, as quite frequently metastases do not occur in the marrow until the patient is too cachetic to produce an adequate reaction.

The blood picture of carcinosis of bone marrow is identical with a part of that in the leucoses (cf. p. 52), and in fact, it is a convenient working hypothesis to regard the blood picture of the leucoses as being compounded of two factors, viz., an emigration of the cells of the true leukæmic foci and a leukæmoid reaction induced by the irritation of the leukæmic infiltrations.

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CHAPTER VII

RETICULO-ENDOTHELIOSIS

It is not possible to give an historical introduction to this subject, because a conception of the reticulo-endothelial system is so very recent, while the pathological conditions affecting this tissue are almost only subjects of conjecture. We have, of course, some knowledge of certain rather obviously reactive states of the reticulo-endothelium, such as that associated with diabetic lipoidæmia, but the present chapter is intended for the discussion of hyperplasias of the reticulo-endothelium in which no increase of functional ability can be detected, although they may be associated with perversion of normal activity.

Those writers who share the view that monocytes are direct derivatives of the reticulo-endothelium, will naturally include *monocytic leukæmia* in the class of leukæmic reticulo-endothelioses ; they would, on the same basis, regard the blood picture of glandular fever as a " leukæmoid reticulo-endotheliosis " ; this classification is, of course, not adopted in this book.

The subject of the histogenesis of Hodgkin's disease has received very little further illumination since the publication of the now classical papers of Sternberg and Reed, who seem to have exhausted the discussion of the histological changes. A brief description of the main features of the microscopic anatomy may be convenient, at this point. Essentially the changes are infiltration and replacement of the affected lymphatic tissue with lymphocytes, " epithelioid " cells, and usually, eosinophilic granular cells ; this new-formed tissue has a great tendency to become cicatricial in the later stages

of its life history. Further, there is a variable number of giant cells of a character rather different from the ordinary foreign-body giant cell. These elements are peculiar to Hodgkin's disease, and possess one or more lobulated nuclei, which are very rich in basi-chromatin ; atypical mitoses in these cells are frequently seen.

It is commonly stated (Fraenkel) that the new-formed tissue compresses and pushes aside the normal lymphatic tissue, but this does not really quite correspond with the appearances of the lesion. It is found that, in the early stages at any rate, the lymphadenomatous tissue is intimately mixed with the lymphatic, giving the impression that it has arisen from some tissue or cell-type widely diffused in lymphatic tissue. By increase of the lymphadenomatous tissue, the normal structures can be compressed and obliterated, but the early stage is a diffuse infiltration.

The series of changes is, thus, as follows :—Increase in number of lymphocytes and endothelial (" epithelioid ") cells, appearance of giant cells, excess of fibrillar tissue, and atrophy of the cellular components. These changes are admitted by all writers, but it seems to be possible to make out rather more detail of the processes at work.

In the earliest stages it is not difficult to note that the number of lymphocytes is definitely excessive, while the ordinary arrangement of the glandular tissue is deformed or obliterated ; at this time there is also excess of endothelial cells, but only of slight degree. Quite soon the endothelial cells increase in number, and the lymphocytes become less excessive, while a certain amount of non-cellular fibrillar material becomes noticeable. Still later the lymphocytes become very scanty, the endothelial cells by no means numerous, and the fibrils fill the greater part of the picture. The typical giant cells are most numerous at the stage when endothelial cells are most excessive. Infiltration of the tissue with eosinophilic granular cells is not necessarily to be regarded as an essential part of the morbid process, nor is it

even certain that these cells are really myelogenous leucocytes identical with those of the circulating blood.

There have been many writers who have supposed that eosinophilic granules arise as the result of ingestion of various foreign particles, *i.e.*, are not cytoplasmic differentiations of the same degree of specificity as are the neutrophilic granules. Weidenreich has vigorously contended that eosinophilic granules are nothing more than small particles of degenerate red cells which have been taken up by lymphocytes whose nucleus has become polymorphous as a result of this phagocytosis. Sternberg has attacked this conception by pointing out that particles of red cells can often be seen lying among the granules of eosinophilic granular leucocytes, but are always clearly distinguishable from them; he came to this conclusion when repeating some experiments of Weidenreich. This author had injected red corpuscles into the peritoneum, and from the results came to the above-mentioned conclusions. Sternberg carried his attack a stage farther by pointing out that in such peritoneal exudates no mononuclear cells with eosinophilic granules were present; only ordinary polymorphonuclear forms could be found; this would imply, on Weidenreich's theory, that the lymphocytes, which were about to take up portions of degenerate red corpuscles, developed polymorphism of the nucleus before they became granular. This is difficult to imagine, and in any case, no polymorphonuclear, but non-granular cells could be found.

Ringoen has shown that the eosinophilic granules of the cell are truly endogenous formations, but has adduced evidence that the cell may arise in connective tissue, *i.e.*, is not necessarily always a myeloid cell.

We seem to be presented with several possibilities to explain the occurrence of infiltration of lymphadenomatous tissue with eosinophilic granular cells:—

It might be that lymphadenoma is due to a metazoan parasite, because it is well known that such infestations are

commonly associated with eosinophilia in the blood and tissues (p. 121); the infiltration might, however, have no special aetiological significance, but result from a perversion of the activity of the reticulo-endothelium, *i.e.*, as a sort of myeloid metaplasia; this is not very likely, because no other example of myeloid metaplasia resulting in the formation of only one type of granular leucocyte is known; the eosinophilic granules may not be the ordinary myeloid type, but may occur as the result of ingestion of hæmoglobiniferous particles; they would then correspond with the eosinophilic granular cells described by Weidenreich.

It is clear that in the absence of further information we cannot include these cells in our histogenetic discussion.

A picture of the histogenesis of lymphadenoma, which appears to be fairly complete in its details, is as follows:— The early increase of lymphocytes must presumably depend upon excessive activity of the parent tissue, which we have already decided is the reticulo-endothelium.

The "endothelial" cells, which are increased in number, even in the early stages of the disease, are thus really proliferated, lymphocytopoietic reticulo-endothelial elements.

A progressive degradation of the character of the reticulo-endothelium (possibly due to persistence of excessive activity) results in a diminution of lymphocytopoietic activity, and an increase in the number of "endothelial" cells, which seem to proliferate more and more as their lymphocytopoietic power fails.

It is sufficiently well recognised that endothelial cells can, in conditions of excessive demand upon their functional ability, give rise to giant cells. These may develop by fusion of adjacent cells, as in the case of the ordinary foreign-body giant cell, or by nuclear division and cytoplasmic overgrowth of a single cell. The latter seems to be the mode of development of the lymphadenomatous giant cell.

The power of forming fibrils persists, even in the most over-taxed "endothelial" cell, and an excessive development

of reticulum seems to be associated with persistence of demand upon the powers of the cell ; this represents the last or cicatrical stage of the lymphadenomatous lesion.

Such an account of the histogenesis of the lesions of Hodgkin's disease leaves little room for doubt as to the very essential participation of the reticulo-endothelium in the process ; an extraordinary case recorded by Schultz, Wermbter and Puhl illustrates this fact. These writers describe a case of giant-celled granuloma in which the large cells contained both fatty and iron-containing substances, *i.e.*, obviously the cells belonged to the great storage system of reticulo-endothelium.

It has already been mentioned that the reticulo-endothelium has important functions in protein metabolism (Kuczynski), and, therefore, in the formation of amyloid (Jaffe). It is, thus, not surprising that amyloidosis may accompany lymphadenoma, even in the definite absence of tuberculosis.

There are a few cases on record in which lymphadenomatous changes in the lymphatic tissue were associated with a leukæmic or sub-leukæmic blood picture and typical myelotic changes in the hæmatopoietic tissues. It is not likely that such cases represent a co-incidental occurrence of the two diseases. Ziegler is of opinion that they occur as a result of compensatory replacement of the injured lymphatic cells by myeloid elements, but it is difficult to understand how two such totally different tissues can hypertrophy as compensation for one another. It is much more probable that the same noxa which caused the atypical proliferation of lymphatic tissue has caused similar changes in the marrow. (Catsaras). More than ever are we confirmed in our belief that the reticulo-endothelial system is an entity which differs in different places only on account of its environment ; but also we receive much support for the view that Hodgkin's disease is to be regarded as a reticulo-endotheliosis.

There is yet more evidence available to support our conception of the nature of this malady. There are known to be cases of lymphadenoma in which the clinical course is comparatively rapid, and the histological changes indicate a much greater degree of cell activity than usual; so well marked are these changes that they are often known as "Hodgkin's sarcoma." In the histological characters of this pathological condition we can find further evidence for the belief that the lymphadenomatous process starts in the reticulo-endothelium. Ewing has shown that the greater malignancy of some cases of the disease is associated with involvement (possibly primary) of the reticulum of the thymus, although this fact does not otherwise modify the histogenetic process. The thymic reticulum cannot be regarded as being of epithelial origin, but must represent the lymphocytopoietic mechanism of the organ, *i.e.*, it is reticulo-endothelial in nature. Ewing, in his monumental book on "Neoplastic Diseases," also describes a condition of "reticulum-cell sarcoma," which appears to have all the histological characters of acute Hodgkin's disease. This term "reticulum-cell sarcoma" is not in common use, and the tumours which Ewing designates in this manner are usually known as malignant endotheliomata. I have been able to show that the power of formation of fibrils is common in the solid "endotheliomata," and, annoying though the confused terminology may be, it seems, by its very existence, to show that all these conditions are closely allied and of the same histogenetic type.

The existence of such "sarcomatous" forms of Hodgkin's disease is not enough evidence to permit one to agree with Yamasaki that all cases of the malady are neoplastic in nature. I can equally see nothing to support the view of Tsunoda that lymphadenoma is a neoplasm with a primary growth in one area of the lymphatic system, and multiple metastases, which ultimately cause a pseudo-systematic involvement of the whole of the lymphatic tissue of the body.

The view of St. Klein that lymphadenoma is closely allied to lymphatic leukæmia is, in a limited sense, true if an origin of the histological changes from reticulo-endothelium is admitted.

The ætiology of the disease is still quite unknown ; and it is not possible to agree with Sternberg that all the cases are due to tuberculous infection, fully or incompletely virulent. Admixture of the lymphadenomatous process with tuberculosis is by no means rare, but the relationship of the one to the other is not known. Even the frequent occurrence of the so-called Much's granular stage of the tubercle bacillus in lymphadenomatous lesions is scarcely sufficient evidence of an ætiological relationship to tuberculosis. It is, however, necessary to point out that injection of emulsions of lymphadenomatous tissue, in which Much's granules have been found, into guinea-pigs has resulted in the development of tuberculosis, although no signs of such infection were histologically detectable in the human lesion.

A number of bacteria of various kinds have been regarded as the cause of lymphadenoma (Yates and Bunting, Negri and Miremet), but transference to animals, as a result of injection, has always been unsuccessful.

The blood changes occurring in Hodgkin's disease are far from spectacular, except in the rare cases of involvement of the marrow.

Leucocytosis is almost invariable, and there is no other disease (in which clinical evidence of infection is absent) in which a very high number of leucocytes can persist for so long a time. Neutrophilia is the main cause of the leucocytosis, although the absolute number of eosinophiles may be above normal. The lymphocytes are reduced in number, probably as a result of the destruction of lymphatic tissue. Monocytes are almost always increased, and are, quite frequently, more numerous than the lymphocytes.

There are, however, cases accompanied by leucopenia (about 20 per cent. of cases, according to Fabian), but in

them toxic changes in the nuclei of the neutrophiles are usual.

Eosinophilia of well-marked character is not very common, but may reach quite considerable figures ; usually this occurs in company with well-marked leucocytosis.

The red corpuscles are rarely much reduced, and may, in cases with cyanosis and dyspnœa due to compression, rise above normal figures. Severe anæmias may occur in the acute cases.

The blood changes occurring in those cases in which lymphadenomatous deposits are present in the bone marrow resemble the picture seen in association with secondary neoplasia of the marrow, *e.g.* :—

Red corpuscles . . .	4,650,000 per c.mm.
Hæmoglobin	90 per cent.
Colour index	0·97
Leucocytes	45,000 per c.mm.
Polymorphs	75 per cent.
Myelocytes	4 ,,
Myeloblasts	15 ,,
Lymphocytes	6 ,,

The blood picture included some polychromasia, etc., but nucleated red cells were not seen.

The absence of any great degree of interference with erythropoiesis is to be expected in a malady in which the essential feature is formation of hyperplastic reticulo-endothelium, which is an extra- rather than an intra-vascular process ; erythroblasts in small numbers do sometimes appear in the circulation in advanced cases of lymphadenomatous infiltration of the bone marrow.

We can conclude with the view that lymphadenoma (Hodgkin's disease, lymphogranuloma, etc.) is a malady affecting the reticulo-endothelium ; at first it involves only a circumscribed area, but later becomes more generalised, *i.e.*, it is not claimed that this is a systematic disease. Incidence of the lesion in different areas of the lymphatic

tissue of the body results in different clinical pictures, but the pathological appearances seem to form a well-defined entity.

In the absence of knowledge of the ætiology of the disease, the older methods of treatment with arsenic and with X-rays comprise the best that can be offered.

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CHAPTER VIII

"POLYCYTHÆMIA"

Some introduction in the form of an attempt at making a clear classification of the terms to be employed is an essential preliminary to this chapter. The term polycythæmia is often used to denote conditions associated with increase in the number of circulating erythrocytes, but there are grave objections to placing them all in one class.

There are two main groups of pathological states in which increase in the number of circulating red corpuscles is an essential feature: A persistent increase of red corpuscles of unknown origin; this can well be termed *erythræmia* in conformity with the terminology adopted in the discussion of the leucoses; the second group contains those cases in which an increase in the number of circulating red corpuscles results from the action of a known stimulus, such as breathing air with low oxygen tension at high altitudes. Such states can very well be termed *erythrocytoses* (or erythræmoid reactions), again in conformity with the terminology adopted in the case of increase of leucocytes. It is really to the consideration of erythræmia that this chapter is devoted.

The clinical features of erythræmia are striking, but can be simulated by various pathological erythrocytoses, although the latter rarely cause such a well-marked symptom-complex. The reddish colour (less blue than that of cyanosis) of the skin and mucosæ, the tendency to bleeding from the gums, and the severe attacks of vertigo are usually the earliest signs to attract notice.

The number of red corpuscles per cubic millimetre of blood is increased to nine millions or more, and the leucocytes are

usually excessive, *e.g.*, 15,000 to 30,000 per cubic millimetre. The hæmoglobin is also increased, but not to such a great extent as are the corpuscles, and, therefore, a low colour index is the rule. The total blood volume is definitely increased, and, therefore, the number of red corpuscles in the body is even more excessive than would be imagined from an ordinary enumeration of them.

Albuminuria and nephritis of slight degree are quite common, but casts are usually very scanty. Blood pressure is often raised; this presumably arises when the dilatation of the vessels to the requirements of a very viscous blood has reached its maximum. If this explanation be correct, there is no need to classify cases with high blood pressure separately as has been done by Gaisböck.

Enlargement of the spleen, which may be very great, is usual, but may be absent for a long time.

The polycythæmia depends upon greatly excessive erythropoiesis in the bone marrow, which is always found to be bright red and excessively cellular. It is often stated that there is no justification for applying the name erythræmia to the condition, because although there is great increase in the number of circulating corpuscles, they are essentially normal and mature elements. I can confirm the statement of Minot and Buckman that this is certainly not the case, but it is admittedly much easier to detect the signs of immaturity in leucocytes than in red corpuscles. Polychromasia is quite common, but is usually only slight, although it varies from time to time in the same case. Reticulated red corpuscles which are admittedly young forms are always present in numbers greater than normal. There is always variation in the strength of the staining affinity of the corpuscles, and this is presumably due to their different ages. In addition to this anisochromia, there is usually also a slight degree of anisocytosis.

The hyper-activity of the marrow is not confined to erythropoiesis, but extends to the leucocyte-forming mecha-

nism, as is shown by the leucocytosis in the blood, and the leucoblastic reaction in the marrow. The leucocytosis is not a simple increase of mature myeloid leucocytes, but is always associated with the appearance of some immature granulocytes, *i.e.*, has the characters of a leukæmoid blood picture. Even the mature forms show deviations from normal structure, such as variation in size and atypical lobulation of the nucleus, while incomplete granulation is quite common. The platelets are also increased in number, and often excessively large ones are present, while megakaryocyte nuclei can commonly be found, even if only in minute quantity.

It must be admitted that the appearance of general immaturity of the blood picture in erythræmia is less extreme than in myelosis. This, I think, is not very surprising when it is remembered that the erythropoietic mechanism is a more stable one than is the leucopoietic; this is seen very clearly when experimental attempts are made to stimulate one or the other; leucocytosis is easy to produce, but erythrocytosis in the form of excessive new formation of red corpuscles is not easy to effect. The difficulty of influencing the rate and intensity of production of red corpuscles is unpleasantly well seen in the attempts at treatment of anæmia. We should have to look for signs comparable with those of myelosis only in very advanced cases of erythræmia; then it is found that blood-formation is very much more disorderly; and even extra-medullary blood-formation (myeloid metaplasia) occurs, just as in myelosis. This stage is not often reached, because the patient dies of some such complication as cerebral thrombosis before his erythropoiesis has become completely disordered.

Minot and Buckman have done excellent service in putting on record the occurrence of anæmia in three cases of polycythæmia, which had all the usual signs and symptoms of erythræmia for many years before. The red corpuscles fell from over eight million to about three million within a year;

at the same time there occurred a further increase in size of the spleen. One case developed this change of type about two years before death, and one almost six years before the end, while the third case was still living at the time of their publication and had undergone the alteration about two years previously. These writers state that a "pernicious" type of anæmia occurred in each of these cases, with much anisocytosis and poikilocytosis. That the picture was not exactly that of pernicious anæmia is shown by the very high numbers of erythroblasts, which at times exceeded 3,000 per cubic millimetre. Many corpuscles containing nuclear remnants of various shapes were present, and polychromasia was often extreme. The number of erythroblasts and other immature forms increased progressively as the end of the disease got nearer. The number of leucocytes also tended to rise, and all forms of immature myeloid cells appeared; many of these were so abnormal as to be unrecognisable as any usual type of cell. Only one autopsy was possible, and the changes, both macroscopic and microscopic, were those of chronic myelosis with well-marked myeloid metaplasia in spleen and liver.

The most conclusive observation in connection with the discussion of the relation of myelosis to erythræmia is that of Ghiron, who observed the development of polycythæmia in a typical case of leukæmic myelosis.

We have already discussed the essential features of the leucoses, which are the appearance of both immature and abnormally differentiated leucocytes in the blood; this is the state known as "anaplasia." We have previously reached the conclusion that red corpuscles and granulocytes are derived from a common ancestral tissue; the reticulo-endothelium. It is not surprising, therefore, that a malady in which this tissue is involved should present evidence of disorder of both its functions. It is, of course, quite impossible at present to explain why erythropoiesis should predominate in some cases, and leucocytopoiesis in others,

but the very fact that the one picture may merge into the other seems to be excellent evidence of the essential identity of the two processes.

It is not clear by what mechanism the anæmia develops, but it seems certain that the original polycythæmia does not arise as a result of defective blood destruction. No doubt increased activity of the hæmolytic mechanisms of the body follows the excessive production of red corpuscles by the hyperplastic marrow; and it is possible that the anæmia arises as a result of a sort of over-compensation in which the destructive mechanism becomes too powerful. It is, however, much more probable that the anæmia arises, at least partly, as the result of some change in the process of erythropoiesis; possibly it is due to progressive exhaustion of the erythropoietic power of the reticulo-endothelium. The increase in the size of the spleen in the three cases of Minot and Buckman, which developed anæmia, suggests that an increase of hæmolysis had also occurred; it is very doubtful whether the amount of myeloid metaplasia found in the spleen could account for its great increase in size.

Of extraordinary interest is that polycythæmia may have a familial incidence; Engelking has described five cases in one family in three generations. Each of the patients showed a somewhat infantile appearance and had various peculiarities, attributed to endocrine disturbance. Doll and Rothschild record four cases in one family (with Huntington's chorea). When it is remembered that leukæmia may also show a familial incidence (Schereschewsky), another resemblance between the two conditions is brought forward.

The particular form of erythræmia described by Gaisböck deserves separate description, although many writers are not at all satisfied that it must be put in a special sub-group.

The majority of cases of erythræmia are associated with great splenomegaly, and the blood pressure is often normal for long periods of time. Gaisböck pointed out that there are cases in which polycythæmia of unknown cause occurs

without notable enlargement of the spleen, and with rise of blood pressure; this is the so-called "polycythæmia hypertonica." He states that apoplexy occurs with great frequency in this form of polycythæmia, while it is rare in the more usual type; he records the development of the disease in persons who had previously had an apoplectic seizure.

It seems highly probable, as Eppinger suggests, that polycythæmia hypertonica represents the effects of erythræmia in persons with renal arterio-sclerosis. The absence of notable splenic enlargement can scarcely be regarded as a definite differential feature, because both Senator and Stern have described ordinary cases of erythræmia in which splenic enlargement was found only at autopsy.

The *treatment* of erythræmia is far from satisfactory; no medicinal measures produce more than alleviation of the symptoms.

Large doses of arsenic (Türk) may produce temporary clinical and hæmatological improvement, associated with decrease of the splenomegaly.

Benzol, which is known to retard cytopoiesis in the marrow, has been used by Kiralyfi, who in this way caused reduction of the number of red cells and diminution of the size of the spleen.

There is a good deal of experimental work dealing with the effects of poisoning with phenylhydrazine hydrochloride, and all of it suggests that one of the main effects of this substance is a destruction of red corpuscles, either directly or indirectly. Eppinger has used this poison in the treatment of erythræmia with some good result. He uses subcutaneous injections of phenylhydrazine hydrochloride in 1 per cent. solution. The first dose is 2 c.c. of the solution, and gradually this is increased to 7 c.c. Continual examination of the blood is very necessary, but with careful control he has managed to reduce the number of corpuscles in one case from 8,900,000 to 3,600,000, and in another from 10,500,000 to 4,000,000.

This method of treatment is by no means free from risk, and may cause a very severe anæmia, if the dose be too large or too frequently repeated.

Splenectomy has been tried in some cases, but without success ; this is exactly what would be expected when it is remembered that polycythæmia may follow removal of the spleen.

Treatment with X-rays is commonly employed, but it seems that the spleen should not be exposed to the rays because the end-effect will be atrophy of the organ, and will, therefore, result in changes similar to those following splenectomy. Radiation of the long bones, however, does produce beneficial results, and should form part of the treatment of every case.

The suggestion made by Gaisböck that extensive surgical removal of marrow tissue should be carried out, is not to be accepted, because it is well known that such extirpation is followed by regeneratory processes of extreme activity.

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CHAPTER IX

"HÆMORRHAGIC DIATHESES"

It is freely admitted that the term "hæmorrhagic diatheses" is far from being satisfactory, but, as will be seen later, so little is known of these conditions that a very non-committal title is essential. The name is here applied to a variety of morbid states which have in common a tendency to the occurrence of hæmorrhages, either in the form of petechial spots, purpuric extravasations, or ordinary loss of blood from free surfaces. A number of diseases characterised by purpura are described under various names, and it will serve our purpose best to discuss each one separately before attempting to form some classification of them.

The first of these disease-states to be described is that best known as **Werlhof's Disease.** This term implies the acceptance of no special ætiological theories. It is well, however, to mention some of the commoner synonyms of the malady, although, as will be seen later, not all are really suitable; it is known as "essential thrombopenia" by Frank, "thrombocytolytic purpura" by Kaznelson, "hereditary hæmorrhagic thrombasthenia" by Glanzmann, "purpura thrombopenica" by Schultz, "hæmogenia" by Weil, and as the "hæmogenic syndrome" by Roskam.

This disease, which is rarely either familial or hereditary in its incidence, occurs in otherwise healthy persons, and is characterised by periodical hæmorrhages into or from the tissues; the course may be chronic, but is often markedly intermittent. The attacks occur at times when there is great reduction in the number of blood platelets (thrombocytes) in the circulation; in association with this there is a fairly

typical clinical picture, which was described by Werlhof in a form that is still acceptable. The essential feature is the occurrence of the hæmorrhages for no detectable reason ; the tendency to bleeding is, as a rule, not a persistent one, and normal conditions return in days, weeks or months. In the intervals, the patient appears to be perfectly healthy and the blood changes associated with the occurrence of the attacks disappear completely. This typical disease is, however, not so common as a more chronic form in which remissions from the bleeding occur without return of the blood picture to normal. There is also a more severe form in which remissions are incomplete, and the patient continually suffers from a tendency to hæmorrhages, which is at times only slight, and at others severe. In the typical form of the malady the remissions may last for months or even years, and during these times the patients can sustain the ordinary injuries of everyday life or of sports without differing from normal in their reactions, *i.e.*, there are periods of complete freedom from any sign of the disease.

The disease seems to be diagnosed less frequently than should be the case because it is usually expected that a purpuric rash must accompany the exacerbations ; this is by no means the case ; the malady is a hæmorrhagic one, but not necessarily a purpuric one. One of the most striking, perhaps the most essential, characters of the malady is the ease with which hæmorrhages can be caused, and their persistence when once induced. The latter tendency is demonstrated by the increased " bleeding time " after small incisions in the lobe of the ear (Duke). Hess and Frank introduced another valuable test by which " purpura " can be artificially produced in sufferers from the disease, even when no spontaneous purpura is present. Venous congestion of the arm is produced by the application of a tourniquet for ten to fifteen minutes ; arterial hyperæmia, induced by hot air, is an advantage, if it can be procured at the same time. In Werlhof's disease, subcutaneous hæmor-

rhages varying in size from a pin-head to a lentil occur; in severe cases a generalised petechial exanthem may occur on the whole of the arm distal to the bandage. Even the use of the percussion hammer over bony prominences may result in the occurrence of definite bruises. It is not necessary for all three of these tests to be positive in order to arouse a grave suspicion of the presence of Werlhof's disease, but at least one of them is always present.

The essential feature of the blood picture during the exacerbations of the illness is decrease in the number of platelets (thrombocytopenia). Not only are the platelets diminished, but those that are present differ from normal in size and shape. Giant platelets are quite commonly seen, and are very characteristic. As a result of the thrombocytopenia, clotting of the blood *in vitro* takes only the normal time, but the rate and degree of retraction of the clot are defective.

The origin of the thrombocytopenia is best discussed at the same time as the morbid histological changes are described. The difficulty in determining the mode of origin of the platelets makes the present task more difficult, but the histological appearances of the marrow in Werlhof's disease very strongly support Wright's view that these elements are derived from megakaryocytes. Seeliger was able to show that following injections of peptone the granules of the protoplasm of the megakaryocytes underwent a redistribution. They tended to become collected into small groups, which, although still lying in the cytoplasm, looked exactly like platelets. The amœboid power of the megakaryocyte also became more marked after the injections, and long cytoplasmic processes filled with granules were seen. In this connection the occurrence of giant platelets in Werlhof's disease is of great interest; these presumably represent masses of platelets, which have been hurried out of the marrow before they were quite mature. Kaznelson has even been able to find a complete megakaryocyte in the peri-

pheral blood, and in it the granules were collected into groups in the cytoplasm in a manner exactly simulating the ordinary platelets.

The fate of the blood platelets, even in health, is not really clear, but there seems to be no doubt that the reticulo-endothelial system, particularly in the spleen, plays a great part in their destruction. Kaznelson has made this view the central pillar of his theory of Werlhof's disease, which he believes to be due to a primary hyper-function of the spleen, which may occur in association with an intact bone marrow performing normal hæmatopoietic functions. It is for this reason that he terms the disease "thrombolytic purpura." He bases his view on several features which he states are characteristic of the malady :—

(*a*) The not infrequent occurrence of splenomegaly, which he regards as being due to excessive functional activity.

(*b*) He has observed excessive numbers of megakaryocytes in the marrow in cases of symptomatic thrombocytopenia (*e.g.*, streptococcal septicæmia) ; and also he has noted that in these circumstances megakaryocytes occur in the splenic pulp. Similar appearances are invariable in Werlhof's disease, and he supposes that the increase in number of megakaryocytes in the marrow is a compensatory phenomenon, but will not admit that those in the spleen arise as a result of myeloid metaplasia. He regards the splenic megakaryocytes as being the result of embolic lodgement, *i.e.*, their presence is indicative of a myeloid compensatory reaction so vigorous that even the parent cell of the platelets emigrates into the circulation.

(*c*) He claims that the number of platelets in the spleen in this disease is greater than would be expected from the amount of blood in the organ. This he attributes to retention of the thrombocytes in the organ, rather than to formation in its pulp.

(*d*) The great rise of platelets following splenectomy can, according to this writer, only be attributed to the removal of

the great thrombolytic organ. He appears to presume that the spleen when presented with normal platelets will destroy them in excessive numbers, and compares this state of affairs with that seen in hæmolytic icterus ; this cannot properly be done because in the latter disease the spleen is being presented with abnormal corpuscles, *i.e.*, one is not dealing with a primary hyper-splenism.

Frank has adduced strong evidence that there is a real defect in the production of platelets, which he attributes to the action of some noxa on the megakaryocytes alone. It is known that normally the whole myeloid tissue reacts vigorously to any severe hæmorrhage ; evidence of this is seen in the blood in the presence of immature erythrocytes, leucocytosis and increase in the number of platelets. Splenectomy, in the majority of cases of Werlhof's disease, is followed by similar changes ; and it is to the increase of platelets after this operation that the clinical improvement is due. Frank, however, has been able to observe cases in which splenectomy has resulted in the development of leucocytosis and of increase of red corpuscles without a concomitant rise in the number of platelets. Further, the rise of platelets, which usually occurs after splenectomy in this malady, is not always a permanent condition of the blood ; there may be gradual return to the thrombocytopenic state. The latter phenomenon could be explained, on Kaznelson's hypothesis, as the result of compensatory hyperplasia of some platelet-destroying mechanism, which would thus be replacing the loss of splenic tissue ; such a suggestion would, however, not meet the state of affairs in the cases where no thrombocytosis follows splenectomy. There really does seem to be strong evidence pointing to a pathological condition of the platelet-forming mechanism without any associated lesion of the rest of the myeloid tissue. Seeliger has described pathological changes in the protoplasm of the megakaryocytes in a case of Werlhof's disease ; there were many of these cells (about 90 per cent.) in the marrow in which no

granules could be found; about 6 per cent. were only partially granular, while the remaining 4 per cent. appeared to be normal. These changes presumably represent a relatively severe stage of degradation of thrombocytopoiesis, and doubtless more subtle alterations also occur. There is clearly a defect in the normal separation of the platelets from their parent megakaryocytes, as is shown by the presence of abnormally large forms in the blood. There can be but little doubt that many of these giant thrombocytes are really several platelets, which have separated off from the cytoplasm of the megakaryocyte as a single mass instead of arising separately. The non-granular megakaryocytes may represent cells which have suffered from the action of some toxin, but it is equally probable that at least some of them are really immature cells (megakaryoblasts) in which granules have not yet developed. There can be no doubt that the platelet-forming mechanism is a very delicately balanced one, as is shown by the experiments of Duke, who was able to cause practically complete disappearance of platelets from the blood by administering benzol, although the leucocytes and red corpuscles were not altered in number.

The acceptance of the view that the megakaryocyte is the site of first injury in Werlhof's disease does not involve a denial of the importance of excessive splenic function; it only involves a repudiation of the conception that such an alteration is the primary fact.

The *therapeutic measures* available in this disease are comparatively successful, but cannot be regarded as being really satisfactory in the absence of a knowledge of the ætiological factors. It is obvious that the essential of all treatments is the production of an increased number of platelets. Duke has shown that in cases with no platelets in the circulation, a rise even to 10,000 per cubic millimetre quite definitely and beneficially influences the hæmorrhages. Numbers above 30,000 or 35,000 are usually associated with complete dis-

appearance of the tendency to bleeding, and even artificial production of hæmorrhages is difficult.

The number of platelets can be increased by transfusion of normal citrated blood; in this way the numbers in the patient's blood can be increased to about 30,000 per cubic millimetre, if some 250 c.c. of blood be supplied by the donor. The increase persists only for a few days on account of the rapid destruction of the elements which have been introduced into the circulation. It is important to realise that in some cases another result in addition to the simple mechanical increase of thrombocytes occurs; this is the effect of stimulation of the formative cells, and manifests itself by a spontaneous and more or less persistent increase of platelets (thrombocyte crisis). One cannot hope, however, for any permanent increase after transfusion, and, therefore, only temporary amelioration of symptoms will be brought about in this way, but the transient results may be excellent.

The one almost certain method of inducing the onset of a thrombocyte crisis is found in splenectomy; the resulting crisis may cause an apparently permanent increase of platelets or, more rarely, a temporary one. The first splenectomy in this disease was performed at the suggestion of Kaznelson, who expected that it would yield satisfactory results, because, as has already been mentioned, he believes that the spleen is the site of the essential lesion.

The cases can be arranged into three groups according to their response to splenectomy :—

1. Those in which the operation is followed by a rapid and persistent rise of the thrombocytes to normal, or even to higher figures. Numbers enormously in excess of normal may occur within a few days of the operation; Naegeli records a case in which the thrombocytes rose to 1,600,000 per cubic millimetre after splenectomy. In these cases the figures gradually fall to normal values, and continue to drop. Cori saw such a thrombocyte crisis, which had been induced by splenectomy, gradually fall to 23,000 per cubic millimetre in

nine months; this very low number did not fall further during the next two and a half years, but it seems very probable that we cannot claim a cure of the condition in any case.

2. Cases in which the number of platelets rise to figures above normal within a few days of the operation, but in which they fall below the critical value (*i.e.*, number at which they are sufficient to prevent symptoms) in a very short time. The platelet-picture in the blood is not, however, quite the same as that before operation, inasmuch as there is a great tendency to spontaneous variation in the numbers, so that they are sometimes above and sometimes below the critical value. In this way a case with persistent symptoms may be converted into one in which remissions and exacerbations occur.

3. Cases in which splenectomy causes no or practically no change in the number of platelets. The very existence of such a group of cases seems to be sufficient evidence that the spleen is not the site of the essential pathogenetic process.

Injection of various protein substances also acts as a stimulant to the bone marrow with a consequent neutrophilia and thrombocytosis (Pentimalli). In the marrow there is histological evidence of great activity, and megakaryocytes are definitely increased, while the number of their amœboid processes is also above normal, *i.e.*, there appears to be vigorous thrombocytopoiesis. It seems reasonable to suppose that some such line of treatment would be of value in Werlhof's disease.

Gram and also Cori have published observations dealing with the results of treatment by injection of milk. The former writer describes a case in which the platelets rose from 4,000 to 57,000 per cubic millimetre within a few days of the first injection, and increased to 190,000 after a second one; a third injection is said to have made the cure a permanent one, but no details of the length of time of later observation are available.

This method of treatment by protein shock does not always result in improvement. Cori and Frank record cases in which no alteration in the number of platelets could be detected after injections of milk. It is interesting to find that patients who do not respond to protein therapy are also not benefited by splenectomy.

It seems highly probable that blood transfusion, which may cause a "platelet crisis," acts by the introduction of foreign protein as well as by simple addition of thrombocytes to the patient's circulation.

Injections of adrenalin are followed, in normal persons, by a lymphocytosis, which passes over into a neutrophilia and a thrombocytosis (Schenk). Injections into sufferers from Werlhof's disease have similar results, but are necessarily very transient, although Frank reports that several injections of 1 mg. of suprarenin in one day may cause a more persistent rise of thrombocytes, but in any case it lasts not more than three or four days.

The therapeutic measure from which the best results are to be expected is splenectomy, but as this is an operation of no mean severity it is well to formulate some idea as to the more obvious indications for operation :—

There can be no doubt that surgical treatment is indicated in those cases in which children suffer from chronic anæmia due to continued loss of blood. In such circumstances, operation should not be delayed too long, because of the chance of permanent defects of development arising ; in adults who suffer from continuous or frequently repeated attacks operation is essential, particularly if they pursue some occupation in which minor injuries are likely to occur ; in all cases in which the attacks recur at short intervals it is essential to operate, as otherwise the patient is exposed to all the risks of severe post-hæmorrhagic anæmia. This applies particularly to those cases in which menorrhagia is a striking feature, because in these there is not sufficient time for the patient to recover from the effect of one excessive

loss of blood before another is upon her; operation in acute cases may require to be preceded by transfusion; this should always be done if the red corpuscles are less than two million per cubic millimetre.

It cannot be too strongly emphasised that local operative measures, *e.g.*, oophorectomy or hysterectomy in cases with menorrhagia, are quite useless, and can result only in the transference of the tendency to bleeding to a fresh site.

A *brief summary* at this point will be an advantage, although full discussion is delayed until other hæmorrhagic diatheses have been described. In Werlhof's disease we are dealing with a malady in which the platelet-forming mechanism of the body is disordered. As a result of the deficiency of platelets in the blood, retraction of clot is incomplete, and persistent hæmorrhages occur, either continuously or intermittently. The efficiency of all marrow stimulants in the treatment of the disease indicates very strongly that the thrombocytes are true myeloid elements.

Among the synonyms of Werlhof's disease the term suggested by Glanzmann was included, viz., **Hereditary Hæmorrhagic Thrombasthenia,** but the absence of any hereditary incidence in the great majority of cases has already been mentioned. Hess has recorded cases which he regards as being examples of hereditary Werlhof's disease, and it is obviously very important to determine whether this form of incidence really does exist. In the four cases placed on record by Hess, the lowest number of platelets was 62,000, and in one case was as high as 76,000 per cubic millimetre. This last case needs a little description, because in this way it is possible to show that Hess has been very lax in his conception of the disease. The case in question was a girl who suffered from epistaxis and a petechial and purpuric eruption. Her brother, who had a normal number of platelets, suffered from very obvious hæmophilia, as was shown by the ease with which large bruises occurred and by the

fact that he continued to bleed for ten days after circumcision.

It is clear that these cases differ from the classical Werlhof's disease, but whether they represent a new malady or can be included among any of the known diseases is uncertain. It is certainly tempting to suppose that the girl, whose brother was a hæmophilic, also suffered from the same condition, but there are grave objections to the diagnosis of hæmophilia in the female. It must not be supposed, however, that such a condition is inconceivable, and an explanation of the rarity of its occurrence can be found on Mendelian lines. It is obvious that the hæmophilic tendency is a recessive character which manifests itself only in the male offspring of the daughter of a hæmophilic father. It must be remembered that the human sperm carries either an X or Y chromosome, and there seems to be good evidence that fertilisation of the ovum by a sperm carrying an X chromosome will result in the development of a female from this XX complex. The XY combination will give rise to a male. The chromosomal constitution of the female is thus XX, and that of the male is XY. In the case of the non-hæmophilic daughter of a hæmophilic father, the chromosomal constitution will be XX^h (^{h} indicates the chromosome bearing the hæmophilic tendency), and here X^h is the recessive. If ova from this woman be fertilised by the sperms of a normal man, the offspring will have the following possible chromosomal constitutions :—

XX : Female with no power of transmitting hæmophilia to her sons.
XX^h : Female with power of transmitting the morbid condition, but with no signs of the malady, because the tendency is recessive.
XY : Normal male, and
X^hY : Hæmophilic male.

It seems to be obvious that hæmophilia in active form can occur in the female only as the result of fertilisation of a

woman carrying the recessive factor by a male suffering from the disease. The constitution of such a female would be X^h X^h. There can be no doubt, therefore, that hæmophilia may occur in the female, but is undoubtedly very rare on account of the great infrequency of such a union as that indicated above.

Glanzmann also regards heredity as possibly playing an important part in some cases of " essential thrombopenia," but unlike Hess, does not think that the defective thrombocytopoiesis is the transmitted feature ; he thinks that there is an inherited weakness of the platelets (thrombasthenia). He has recorded his findings in nine families, in some of which an hereditary tendency to bleeding could be detected in three generations. He states that the platelets in these cases, although often not reduced in number, show definite histological evidence of malformation, such as atypical staining reaction of their protoplasm, lysis or pyknosis of their granules, and even disappearance of granularity. He is uncertain whether to regard these changes as occurring in the ready-formed platelet or in its parent-cell.

Very fine morphological changes, such as those to which Glanzmann attributes so much importance, require ample confirmation before they can be accepted as representing the essential factor in the disease, but it is difficult to escape the conclusion that an hereditary form of Werlhof's disease can occur.

In any case it is permissible to regard the *hæmorrhagic diatheses* so far described as depending upon a more or less selective aplasia of myeloid cells. This opinion naturally leads to the inquiry as to whether any more intensive aplastic conditions of the hæmatopoietic mechanism are known to exist, and, although rare, there certainly are such states.

The group of aplasias of blood-forming tissue now to be described are much more severe in their effects, as might be

expected when it is realised that all the hæmatopoietic cells are affected.

These maladies are commonly classed together under the name "aplastic anæmia"; this term is not really satisfactory, because anæmia is usually taken to apply to decrease in the number of red corpuscles, and this is only a small part of the hæmatological picture of these diseases. Frank uses the name "aleukia hæmorrhagica," but the same objection holds good in this case; equally is this so in relation to another synonym, viz., malignant thrombopenia. We shall find that it is essential to employ some term indicative of progressive wasting of all the myeloid elements.

There are three main features of the disease as it is seen clinically :—

A severe anæmia with a peculiar blood picture;

A hæmorrhagic purpuric condition, and

"Diphtheritic" inflammation, followed by septic infection.

Any one of these phenomena may be detected before the others, and so be the most noticeable; this has led to wrong diagnoses in many cases, which have been regarded as severe secondary anæmia with failure of myeloid function, septic anæmia, pernicious anæmia, and even as scurvy.

The patients who have usually been healthy, are extremely pale, and have severe hæmorrhage from one or more mucous surfaces; even the very slightest injury results in bleeding. They always have a great tendency to bleed from the gums, and this can be seen to depend upon the presence of an ulcerative stomatitis of the character of Vincent's angina. Severe septic infection inevitably, and usually quickly, follows the onset of the disease, which prostrates the patient in a few days.

The blood picture is very striking; there is very great and rapidly progressive fall of the red corpuscles, which may reach numbers under a million. At the same time the amount of hæmoglobin is reduced, practically in proportion to the decrease of red corpuscles; the colour index is, therefore,

usually just at or just below unity. It is in stained films that the extraordinary character of the blood becomes obvious; none of the appearances commonly associated with anæmia can be found. The corpuscles vary little in size; there is no more anisocytosis than is normally found in the corpuscles, and poikilocytosis is also absent. No corpuscles show polychromasia or punctate basophilia, and even reticulated ones can practically never be discovered, *i.e.*, no corpuscles showing signs of immaturity are present. Normoblasts are usually also absent, but occasionally one may be seen if a very extensive examination of films be undertaken. As a rarity, one may encounter a case of this disease in which, for a very short time, normoblasts with pyknotic nuclei are present in considerable numbers in the circulating blood; this almost certainly represents a last attempt at regeneration by a dying marrow. The absence of the ordinary signs of regeneration of red corpuscles (polychromasia, etc.) is of much greater importance in diagnosis than is the discovery of a few old normoblasts.

The leucocytes are also very much reduced in number, and not more than one or two thousand may be found in each cubic millimetre of blood; figures as low as 500 have been recorded and are by no means rare. The neutrophiles may form only 5 or 6 per cent. of the leucocytes, while the lymphocytes form 60 to 80 per cent. The neutropenia cannot be due to retention of cells in the marrow as is shown by the fact that injection of such ordinarily positive chemiotactic substances as sodium nucleinate do not result in the appearance of any more of these cells in the blood. Abnormal and immature forms of leucocytes are always absent; in fact, most of the neutrophiles show very well-marked nuclear segmentation. The eosinophiles may be absent, and are always absolutely reduced, even if they are present in normal percentage.

The relative increase in the number of lymphocytes may be accompanied by an absolute decrease, but this is not an

invariable rule. It is not uncommon to find both absolute as well as relative increase of these cells. In any case, their variations in this disease are not of very great importance, and are not associated with aplasia of the lymphocytopoietic tissue. This is shown by the fact that a very definite lymphocytosis follows injection of adrenalin, but the second half of the reaction (the neutrophilia) does not occur (Gorke).

Blood platelets are very greatly reduced, and may be completely absent from the circulating blood.

These are the typical findings, but various modifications may occur, although the essential identity of the different processes can scarcely be doubted. It seems probable that different agents will cause aplasia of the various cells of the bone marrow of different degrees of intensity, and one may expect to find blood pictures indicative of the selective action of the destructive agent. We have already shown that the thrombocytopoietic system is particularly susceptible to benzol, and it seems quite probable that it may be the site of the first and most severe injury in some of the present series of cases. Such a view explains the occurrence of cases which, for varying periods of time, present both clinical and hæmatological evidence of Werlhof's disease, but later develop into the more severe aplastic condition of the whole marrow. These cases in which thrombocytopenia and no other morphological alteration in the blood suggests a diagnosis of Werlhof's disease, although the malady is really the early stage of myeloid aplasia, can be distinguished from "essential thrombopenia." Patients suffering from the latter disease have already been stated to respond to injections of foreign protein by a leucocytosis; in early cases of incipient complete aplasia, the leucocytosis elicited by this means is always defective. It must be remembered that the myeloid response in some cases of Werlhof's disease is very defective, and it seems probable that some of them must really be examples of early aplasia in which the causative agent has disappeared before irreparable injury

had been done to the marrow. The idea of such a selective action on a single potency of the marrow is strengthened by the observation of Helly that an almost complete aleukia may be associated with no alterations in the number of red corpuscles. It seems probable that "agranulocytosis," which is certainly not associated with severe anæmia, may be another example of such selective toxic effect.

It is clear that the blood picture is so striking, mainly on account of the absence of the morphological changes customary in the anæmias; there is also a markedly "negative" character about the physical signs, which can be elicited clinically. The liver and lymphatic glands are not enlarged, and the spleen may even be slightly smaller than normal. The sore tongue of pernicious anæmia is never seen, and the content of the gastric juice in hydrochloric acid is normal (Sternberg), or, at the most, slightly reduced. Urobilinuria occurs only if extensive ecchymoses are present; and nervous signs do not occur unless hæmorrhages take place into nervous tissue.

The *ætiology* of the disease is, in the great majority of the cases, quite unknown, but there is a small group about which some information is available.

One of the most striking ætiological factors is found in the X-rays, and several unfortunate accidents have occurred as the result of their careless or ignorant use; such effects are no longer likely to occur, but the prevalence of the use of deep X-ray therapy in the treatment of malignant disease strongly indicates the need for caution and for a knowledge of the effects of such exposures on the blood.

Essentially the changes in the blood are leucopenia, following a very transient leucocytosis, and absolute lymphocytopenia. After intensive treatment the leucopenia may persist for four or five weeks, but, in the ordinary course of events, the blood does ultimately return to normal.

There seems to be no doubt that irradiation causes leucopenia by two means: the primary leucopenia is due

mainly to destruction of cells in the circulation, but its persistence depends upon injury of the hæmatopoietic tissue. The lymphocytosis, which can be caused by minute doses of X-rays, is certainly due to direct stimulation of the formative tissue ; it can be simulated by the action of sunlight, which is also followed by lymphocytosis (Clark).

The neutrophiles, in the leucopenic stage, are reduced in absolute number, but their percentage remains high.

The eosinophiles fall coincidentally with the lymphocytes, but tend to rise well above normal figures during the period of regeneration ; this rise tends to occur some weeks after irradiation (Heim, Masieri). There is a strange observation recorded by Petersen and Saelhof, who found that eosinophilia occurred in irradiated dogs only if the liver had been included in the treated area.

Changes in the red corpuscles, as the result of irradiation, are slight unless many doses are given. A single exposure has never been known to produce a severe anæmia, but there is no doubt that this may arise after many doses. It is not so much in cases treated with X-rays for therapeutic purposes that grave alterations in the number of blood cells occur, but in those persons who are frequently exposed to their action ; in them the alterations in the blood and formative organs may be very severe, and may even prove fatal.

The most recent study of the blood changes in workers dealing with X-rays is that of Waindrach, which was unfortunately published in Russian. He describes the phenomena in two groups of persons : the one class is composed of the real workers with the rays, and the other consists of attendants and such like adherents of a radiographical department.

In the first group he describes a slight fall of red corpuscles below normal, but he did not observe leucopenia in any one of thirteen workers. Hæmoglobin falls in proportion to the decrease of red corpuscles. Eosinophiles are definitely

increased in number only in persons who have been engaged in the work for a long time.

In the second group the changes were not very well marked, but eosinophilia was quite usual.

The alterations, which occur in fatal cases of aplasia resulting from long and excessive exposure to the rays, are the same as in the cases due to benzol or to unknown factors in the " idiopathic " cases.

Chronic benzol poisoning is a condition of considerable importance in industrial medicine, and was first studied in detail by Selling. He was able to show experimentally that chemically pure benzol was very definitely toxic to marrow cells, and this was the observation which led Koranyi to make use of this substance in the treatment of leukæmia. The disease, as it is seen in industry, occurs mainly in young women working in a benzol-laden atmosphere in rubber works. It manifests itself in not less than three weeks, and not more than four or five months from the time of starting the work. It is essential to realise that, once the pathological process has started, it will probably not be arrested by withdrawal of the employee from this type of work ; indeed, it is not uncommon for symptoms to be absent for several weeks after the girl has left her work.

The clinical picture is identical with that of the " idiopathic " cases. This is true also of the histological changes in the formative tissues.

The malady is not, however, invariably fatal, as is shown by a case recorded by Brücken. His patient, after six months of severe anæmia, returned to an almost normal blood picture and good state of health in a period of about three months.

The megakaryocytes in the bone marrow seem to be particularly susceptible to the action of benzol. Selling was able to produce slight intoxication with this substance, and, in such circumstances, found that the disease ran the course of a simple benign purpura in animals. Teleky and

Weiner have observed similar characters in cases of slight intoxication in man.

The more or less selective toxic action of benzol is shown also by a case of Santesson's in which the blood became practically free from leucocytes, although the red corpuscles were only very slightly reduced in number.

Salvarsan and similar substances rarely cause an identical condition (Frank), and colloidal silver, such as has been used for the treatment of syphilis and gonorrhœa, can also produce these changes (Herzog and Roscher).

The condition of affairs, in these cases and in those of unknown origin, suggests a resemblance to the condition of the blood seen in scurvy. This similarity has been emphasised by Bierich, but, although an extreme anæmia may occur in scurvy, it does not give the same blood picture as do the aplastic cases ; the relatively high number of platelets in the scorbutic cases is a striking difference. It appears that, in scurvy, there is failure of hyperplasia of the myeloid tissue rather than atrophy of that normally present. Further, if not permitted to persist for too long a time, suitable dietetic measures will result in cure.

The pathological changes in the tissues are very striking, and are the same in practically every case. The greater part of the marrow in all the bones is aplastic, but it is not surprising that some areas of practically normal marrow may remain. It is not uncommon to find that the atrophied myeloid tissue has been, to some extent, replaced by lymphocytic infiltration ; this is, of course, quite a common sequel of any atrophic process. The atrophy of the myeloid tissue in the bones is never accompanied by the development of metaplastic myeloid foci elsewhere.

There is practically never even the slightest degree of hæmosiderosis to be detected in any organ, and so there is no reason whatever for regarding the malady as being a hæmolytic anæmia.

Not only can normal blood-forming tissues be caused to

atrophy by these unknown and known agents, but the latter can cause aplasia, even of the intensely hyperplastic hæmatopoietic tissues in myelosis. In such circumstances the lymphocytic infiltration of the marrow may closely simulate the condition seen in lymphadenosis, but there can really be no question of a conversion of the one disease into the other.

The prognosis, except in the mildest cases of benzol and X-ray cases, is extremely grave. It might be expected, therefore, that, if the unknown noxa disappeared from the body in an early stage, even an occasional cryptogenetic case might recover. This does happen very occasionally (Beneke), but no medicinal or other therapeutic measures are known to be of use.

There are several other pathological conditions, which are associated with a hæmorrhagic diathesis, which should be discussed at this point. The discussion of the interrelationship of all these maladies can be left until the end of this chapter.

It is well known that the acute leucoses are accompanied by clinical evidence of a hæmorrhagic diathesis, which can be distinguished from aleukia only by examination of the blood. It is here contended that the cause of this symptom is the same in both cases (p. 177).

One of the most important conditions to be discussed in this connection is the so-called *pseudo-hæmophilia hepatica* of Frank.

It is quite well known that many diseases associated with *widespread destruction of liver tissue* may end with a severe hæmorrhagic diathesis. Examples are seen in acute atrophy of the liver, phosphorus or chloroform poisoning, yellow fever, hypertrophic cirrhosis (particularly when accompanied by splenomegaly), and even persistent occlusion of the bile ducts. The defect in these cases lies in the quality of the clot formed (athrombia of Frank), but is not necessarily associated with a deficiency of platelets.

The condition of "*hæmogenia*," as described by Weil, has been regarded by him and Isch-Wall as dependent upon disturbance of hepatic function. The malady is described as occurring practically only in the female, and is characterised by prolonged "bleeding time" associated with normal or even decreased "clotting time"; a defect of retraction of the formed clot is always present. Little information regarding the disease is available, but its resemblance to hæmophilia is important.

There is a series of hæmorrhagic conditions in which the cause is to be sought in alterations in the walls of blood spaces rather than in their contents.

The most striking example of such a condition is found in **Schönlein's Disease.** This was originally described as a malady in which small purpuric spots appeared in crops, and were associated with swelling, pain and tenderness of joints. Intermissions are quite common, but recurrences are frequent. The purpuric spots have certain well-marked characters; they are often raised above the general surface of the skin, and are often surrounded by a red zone of raised tissue. The middle of such a purpuric spot may be the site of an urticarial wheal. Swelling of the hands, feet, or eyelids is very commonly associated with the attacks. The swelling of the joints cannot, therefore, without further inquiry be regarded as being of rheumatic origin, and the name *peliosis rheumatica* should not be used to designate this malady.

There is good reason for considering at the present juncture that form of **Purpura described by Henoch,** and now known by his name. He stated that the signs were vomiting, colic, and bleeding from the gut. Extremely severe abdominal pain associated with a bile-stained vomit mixed with blood, and with constipation is the rule. Constipation usually ends with the evacuation of a yellow motion stained with blood; this often occurs at the same time as the cessation of the abdominal pain. It is very common for joint swellings and purpura to accompany the intestinal

symptoms, and the course of Henoch's purpura also resembles that of Schönlein's disease in that it is subject to remissions and exacerbations. Further, both of these maladies are, not infrequently, accompanied by hæmorrhagic nephritis.

The great difference between the diseases here under discussion and Werlhof's disease is that in the former the hæmorrhages are not the essential feature, while in the latter condition they certainly are. The **Schönlein-Henoch Syndrome** is characterised by the development of an erythematous urticarial rash, which becomes hæmorrhagic. It is difficult to escape the impression that we are here dealing with an affection of the capillaries, which leads to a transudative and exudative change in the tissues. Such capillary injury would account also for the tendency to hæmorrhage into the urticarial wheals. This conception is supported by the observation that sufferers from the Schönlein-Henoch syndrome do not give a positive reaction to any of the methods of inducing purpura, which are successful in Werlhof's disease. It is, however, possible to precipitate an attack by injection of foreign protein. The disease is thus well named "*anaphylactoid purpura*" by Glanzmann.

The only therapeutic measures indicated are those customary in cases of urticaria.

If the relation to anaphylactic phenomena in general is not admitted, the name suggested by Frank, viz., *hæmorrhagic capillary toxicosis*, is useful in that it indicates the site of the essential lesion.

There is a form of hæmorrhagic diathesis associated with the now well-recognised condition of **Endocarditis Lenta** (sub-acute bacterial endocarditis). This gradually progressive infective and febrile malady is associated with endocarditis (most frequently of the aortic cusps), enlargement of the spleen, progressive anæmia and hæmorrhagic nephritis.

The disease was shown by Schottmüller to be due to a

non-hæmolytic streptococcus, which does not give rise to suppuration. This fact accounts, in part at least, for the peculiar blood picture of the disease. Neutrophilia is usually absent, and, in fact, a relative lymphocytosis is quite common. The inhibition of marrow function is not so complete as in typhoid fever (p. 195), and, therefore, it is easier to induce a neutrophilia artificially. It is common to find a definite leucopenia with both relative and absolute neutropenia. The defence against this particular infection seems to be undertaken by mononuclear cells in the endocardium, spleen and kidney (Kuczynski and Wolf), rather than in the more usual manner by neutrophiles.

The participation of the endothelium in the defence against such slowly progressive infections is accompanied by the presence of large numbers of " monocytes " in the blood (Bittorf, Hess, Schilling). These mononuclear cells have not the same structure as the normal monocytes of the blood. They have a large round or complexly lobulated nucleus. The cytoplasm contains vacuoles of varying size, doubly refractile particles, and fragments of what is apparently nuclear material. It is not very uncommon to find several of these cells joined together into a small syncytium, and there can be but little doubt that they are true endothelial elements. All forms of blood cells, naturally in degenerate form, can be found inside these cells ; it is even common to find remnants of more than one cell in the cytoplasm of these desquamated endothelial cells.

These cells must arise from the capillary walls during the process of obtaining blood for examination, because they are much more numerous in blood from the ear than in that drawn from a vein. This difference is particularly noticeable if the ear is vigorously rubbed before the blood is taken. The endothelial cell cannot become a macrophage without at the same time losing some of its normal function as a bounding structure ; it is this alteration that underlies the tendency to hæmorrhage in endocarditis lenta.

It is commonly stated that the petechial purpuric eruption of this disease, and also the hæmorrhagic nephritis result from the lodgement of emboli. There is, however, excellent evidence that this is not the case. The rash can be caused to appear by tying a tourniquet round a limb. This mode of inducing the appearance cannot be due to the lodgement of emboli. Further, the tendency to the spontaneous development of the petechiæ in dependent parts of the body is scarcely likely to be due to embolism. The appearances of the renal glomeruli, which are all involved in the pathological process, although in somewhat varying degree, indicate injury to endothelium rather than the presence of innumerable emboli lodging in the glomerular vessels.

A hæmorrhagic diathesis develops also in association with many *generalised septic conditions*, which are not accompanied by thrombocytopenia. It seems to be certain that, in such states, we are again dealing with a generalised lesion of endothelium. Such a view is supported by the form of purpura seen in small-pox, *purpura variolosa*, in which capillary injury certainly occurs.

The last form of hæmorrhagic diathesis to be described is that known as **Purpura Fulminans,** which was also described by Henoch. The disease, which seems to be excessively rare, is characterised by the development of extensive ecchymoses on the extremities. The clinical course is very acute, and it is common for the disease to end fatally within four or five days of the first appearance of purpuric spots. The mucosæ are not affected, and no pathological changes, other than those of anæmia, are found at autopsy.

Frank has shown that in this disease there is both injury to capillary endothelium and to the thrombocytopoietic tissue.

The greatest difficulty in the present chapter lies in the attempt at correlating the changes found in the different types of hæmorrhagic diathesis. It seems, at first sight,

highly probable that there is some common histogenetic basis in all the cases.

We have already seen that there are three main groups of these hæmorrhagic conditions, viz., those in which the thrombocytopoietic tissue is injured, those in which the whole of the myeloid tissue becomes aplastic, and those in which the cause of the hæmorrhages is to be sought in changes of the capillary endothelium. A sub-group of the last series of cases is found in purpura fulminans in which both capillary endothelium and thrombocytes show evidence of injury.

Clearly, any explanation of these maladies must be based upon knowledge of the normal formative tissue. We have already regarded the reticulo-endothelium as the common hæmatopoietic tissue, which is capable of giving rise to different types of cells in various environments. The megakaryocyte, just as much as any other blood-cell, is a derivative of the reticulo-endothelium, and, therefore, interference with thrombocytopoiesis might result from injury of the parent tissue or of the megakaryocytes in the marrow. We have evidence that both of these types of disease occur. Essential thrombopenia (Werlhof's disease) can well be regarded as resulting from injury to megakaryocytes and consequent interference with thrombocytopoiesis. The condition in which defective thrombocytopoiesis depends upon injury to the reticulo-endothelium, which is the parent of the megakaryocytes, is the aleukia hæmorrhagica of Frank (aplastic anæmia). It would be expected that, if aleukia hæmorrhagica depends upon severe injury of ancestral reticulo-endothelium, there would at the same time be evidence of general disturbance of myelopoiesis. This is the case, as is seen in the atrophy of all the formative cells in the marrow, and the rapid reduction of the granular leucocytes in the blood. Frank once suggested the term "*myelophthisis*" to apply to aleukia hæmorrhagica, and it is difficult to imagine a better one.

It seems probable, but no direct evidence is available, that the milder condition (essential thrombopenia) can pass over into myelophthisis, or, at any rate, is due to a similar ætiological factor.

The real difficulty lies in correlating those forms of hæmorrhagic diathesis, in which the capillary wall is at fault, with the thrombocytopenic ones. It must be realised that the developmental history of reticulo-endothelium and of ordinary vascular endothelium is very similar, but in post-natal life their structure and function appear to be entirely separate. There are places in which reticulo-endothelium performs the function of bounding vascular spaces (*e.g.*, in the splenic pulp) without, at the same time, losing its characteristic phagocytic properties. It is in such a fact that one can perhaps find some explanation of " hæmorrhagic capillary toxicosis." Foot has been able to show that, in endothelial tumours, vascular and reticulo-endothelium are interchangeable tissues, and goes so far as to suggest that these two forms of mesenchymal differentiation are only modifications of one another induced by different environmental conditions.

If this conception of the occasional interchangeability of ordinary vascular endothelium with reticulo-endothelium be true, one would expect that some pathological condition, in which both are implicated, must exist. This is the case in purpura fulminans in which capillary injury and thrombocytopenia are both present.

It was shown by Selling that the thrombocytopoietic system was more delicate than the other myelopoietic ones, and, therefore, we can accept as a working hypothesis the view that certain mild noxa will produce " essential thrombopenia " by an action on the megakaryocytes of the marrow. The same or similar noxa, in greater intensity, will attack the parent tissue of the megakaryocytes (reticulo-endothelium), and so induce a generalised myeloid aplasia (myelophthisis). Yet more intense stimuli will destroy the

thrombocytopoietic tissue and cause diffuse injury of reticulo-endothelium, together with all other endothelium. This will cause the picture of purpura fulminans, which may well be due to the same cause as myelophthisis, but the ætiological agent must act more acutely. The hæmorrhagic endotheliosis of various infections, particularly of endocarditis lenta, must be due to some toxin with an affinity for all endothelium, but with a greater action upon that of the capillaries than upon that of " reticular " character.

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CHAPTER X

SYMPTOMATIC BLOOD CHANGES

In an accurate sense all alterations in the composition of the blood picture are symptomatic inasmuch as they are indicative of underlying alterations in the hæmatopoietic tissues, but it is convenient to use the term in a less pedantic manner.

Much of the contents of the present chapter is not an account of absolutely recent work, but it is all so very important in its application to clinical medicine that little excuse is needed for the inclusion of a summary of our knowledge of changes in the morphology of the blood in those maladies, which are not commonly called "blood diseases."

The ordinary accounts of the normal blood picture are based on the average appearances of adult blood. It is, therefore, necessary to make reference to the rather different composition of the blood in children and in old age. A most excellent account of infantile hæmatology has been published by Zibordi in monographic form, and should be consulted by all interested in pædiatrics.

The present section should, if possible, be read in conjunction with Chapter V., in which "leukæmoid blood pictures" in general are discussed.

The Blood Picture of Infants.—It is common to find a few erythroblasts in the blood of new-born infants. These persist, as a rule, only for a few days after birth, but polychromasic red corpuscles can be found for a week or two. The polychromasic corpuscles form 0·5 to 2 per cent. of the red corpuscles, while reticulated ones are present to the

extent of about 10 per cent. The number of corpuscles per cubic millimetre is about six and a half to seven millions, and hæmoglobin percentages are above normal (110 to 115 per cent.).

The number of leucocytes is always above that normal in the adult. Figures between 15,000 and 27,000 per cubic millimetre are usual. There is always a very definite shift to the left of the nuclear index of the neutrophiles, and even myelocytes may be present in the peripheral blood.

In the infant the blood picture is more nearly like that of the adult, except that the number of leucocytes is rather higher, viz., 8,000 to 12,000 per cubic millimetre, and there is a high percentage of lymphocytes (50 to 60 per cent.). Benjamin states that plasma cells, in small numbers, are always present in the blood of infants.

An increase of neutrophiles and a decrease of lymphocytes occur as the child gets older, until ultimately the ordinary adult condition is reached.

Monocytes are very numerous in infantile blood (about 15 per cent.), but fall to adult numbers comparatively early.

The **Blood of Old People** does not show any very consistent changes in its morphology, but a reduction in the number of platelets is extremely common.

It is obviously of importance to determine whether any blood changes occur in association with **Menstruation** There seems to be no doubt that a reduction in the number of red corpuscles occurs at the time of menstruation. This may be quite considerable in degree, *e.g.*, a reduction by a quarter or a fifth. It is clear that the diminution of red corpuscles is very definitely greater than could be explained by the menstrual loss of blood. It is not so certain that a rise of erythrocytes before menstruation occurs, although this is often stated. Pölzl records cases in which the red corpuscles rose about a million per cubic millimetre during the day or two immediately preceding the onset of menstruation.

A relative lymphocytosis seems to occur during every menstrual period, and eosinophilia is not uncommon, particularly in women in whom the periods are irregular in onset and excessive in amount.

It has also been shown (Pfeiffer and Hoff, Henning) that there is well-marked reduction in the number of platelets, which fall immediately the menstrual flow starts, and may reach numbers as low as a third of normal. Vogt has shown that petechial hæmorrhages can be induced in menstrual women by the application of a tourniquet, *i.e.*, during menstruation, there is a latent hæmorrhagic diathesis.

During **Pregnancy** there are no invariable changes in the number of red corpuscles. Leucocytosis is common, but slight in most primigravidæ, but is unusual in multiparæ. In all cases there is a very definite shift to the left of the nuclear index of the neutrophiles. Greater degrees of leucocytosis are common at the end of pregnancy, but are probably associated with slight uterine contractions, *i.e.*, are not evidence of true myeloid hyperplasia.

During **Parturition** the leucocytes may reach 20,000 per cubic millimetre, but there are no published records of recent observations available.

There are no distinctive changes in the blood during the **Climacterium,** but a very slight lymphocytosis, which disappears within a few months, is not rare (Rosenbaum).

Each disease about which information or personal observation is available will be described in alphabetical order in its group. The first class to be discussed is that of infective diseases :—

Diphtheria.—A slight degree of anæmia is invariable, but it does not become severe in the absence of complications.

Leucocytosis is almost invariable ; this is due to well-marked relative and absolute neutrophilia. Eosinophiles are decreased, or, in severe cases, absent. Monocytes are usually relatively and absolutely increased.

A bad prognosis is indicated if a low leucocyte count

accompanies severe clinical signs; also the presence of more than 2 or 3 per cent. of myelocytes is a very bad sign.

Injections of anti-diphtheria serum have different effects according to their value in a given case. Thus, in cases in which response to the injection is good, the leucocytosis is temporarily replaced by a leucopenia, which is again followed by leucocytosis, although this is of less intensity than the initial one. Very soon lymphocytosis and monocytosis replace the neutrophilia. In cases in which serum injection is of little value the initial leucocytosis does not disappear, and may, in fact, rise even higher.

Dysentery (Bacillary).—Ewald states that in uncomplicated cases, there is little or no increase in the number of leucocytes, but that there is a tendency to lymphocytosis (about 40 per cent.) together with eosinophilia of comparatively slight degree (about 8 per cent.).

The occurrence of mixed infection is accompanied by the development of an ordinary infective neutrophilia.

Marcovici records similar results, but states that Türk's "Reizungsformen" are usually present in the acute stage.

There seems to be a considerable degree of variation in the blood picture in bacillary dysentery, because Galambos states that the increase in the number of leucocytes runs approximately parallel with the severity of the disease. Lampe also regards leucocytosis with neutrophilia and no increase of eosinophiles as being characteristic. It is, of course, possible that the last two authors were dealing with complicated cases of the disease.

Encephalitis Lethargica.—Knowledge of the blood picture in this disease is very scanty. There seems to be no doubt, however, that a slight leucocytosis does occur, but there are none of the toxic changes in the neutrophiles, which are so very striking in influenza (*q.v.*).

Endocarditis.—The blood changes of endocarditis lenta have already been described in the chapter on the hæmor-

rhagic diatheses. In the more acute ulcerative cases of endocarditis, an ordinary neutrophilia occurs, but even here there is an increase of monocytes of the type seen in normal blood. The increase is often too slight to be of differential diagnostic value, and in any case is much too variable in its occurrence.

Erysipelas.—Neumann and Gundermann have studied the blood changes in this disease, and the following is a summary of their conclusions :—

A. In mild uncomplicated cases the blood picture, in the acute stage, shows moderate leucocytosis with neutrophilia and shift to the left of the neutrophiles. Eosinophiles are practically absent, and lymphocytes are much reduced. Monocytes are not altered. A day or two before the temperature drops there is a critical fall of the total leucocytes.

During convalescence there is a progressive return of the neutrophiles to normal numbers and quality, a reappearance of eosinophiles, and increase of lymphocytes above normal. A very characteristic feature is the persistence of a very definite lymphocytosis (40 to 50 per cent.) for weeks after the temperature has become normal.

B. In severe cases with no complications the acute stage is accompanied by a considerable leucocytosis. Neutrophilia is well marked, and even " young forms " of neutrophiles appear. There is also severe lymphocytopenia and eosinopenia. A critical fall of leucocytes occurs a day or two before the temperature falls. Convalescence is accompanied by persistent lymphocytosis.

C. Severe cases with complications show a blood picture which is more difficult to interpret. The ordinary characters of the blood in erysipelas are present, but other changes are superimposed. The typical curve may, for example, be interfered with by fresh leucocytoses if abscess formation takes place. If erysipelas occurs during the course of scarlatina or during convalescence from this disease, there may be no eosinopenia.

Erythema Infectiosum.—The blood picture somewhat resembles that of scarlet fever in that leucocytosis (usually here only of slight degree) is accompanied by eosinophilia.

Gas Gangrene.—Blood changes of any degree of importance are found only in cases of generalised infection. In such cases methæmoglobin is present in the blood. Very definite anæmia develops, as does also leucocytosis (2,890,000 and 50,000 respectively in a case described by Weitz). The changes in the number of red corpuscles seem to result from hæmolysis, and not from injury to the bone marrow. This is shown by the fact that anisocytosis and polychromasia are well marked, although normoblasts are scanty in the circulation (Lehndorff and Stiefler). Well-marked shift to the left of the neutrophiles is always present, but usually most of the immature forms have the band type of nucleus. Myelocytes and Türk cells are almost always present.

Gonorrhœa.—A slight anæmia always develops; a low colour index is typical, and, of course, results from a reduction of hæmoglobin greater than the decrease of red corpuscles. It is stated that erythroblasts may appear in the blood (Mondschein). There is always slight leucocytosis, and in the presence of complications this may become well marked (20,000 per cubic millimetre, or even more).

Influenza.—The determination of the characters of the blood changes in this disease is by no means easy, because it is not a very well-defined clinical entity, and, in any case, has so great a tendency to become complicated by intercurrent infections.

Citron and Schemenski state that there is slight anæmia, even in the earliest stage, while Alexander contends that a slight initial polycythæmia occurs. He attributes this to concentration of the blood as a result of profuse sweating. It is clear, therefore, that he is not speaking of the very earliest stages, as were the first two authors.

There seems to be no doubt that the leucocytes tend to

be at the lowest limits of normal, or, more frequently, to be reduced even below that level. The relative number of neutrophiles falls, and reaches its lowest level on the day preceding fall of temperature (Naegeli). Toxic changes in the neutrophiles are always present, as is also a well-marked shift to the left.

The eosinophiles are always reduced in number, and may disappear completely. It can be stated fairly definitely that the degree of eosinopenia runs parallel with the severity of the disease.

Alder states that the lymphocytes fall on the first and second days, and then start to rise to figures well above normal.

The monocytes run a numerical course parallel with the neutrophiles.

Plasma cells with cartwheel nuclei are stated by Alder to be invariable in convalescence.

The development of pneumonia may be associated with leucocytosis of the type ordinarily occurring in that disease, but there are cases in which the leucopenia persists in spite of this complication. It appears that the later in the course of the attack of influenza the pneumonia occurs, the greater deviations from the typical influenzal blood picture will arise; whereas, if pneumonia occurs on the second or third day, the characteristic blood picture of the underlying disease persists. In other words, as the inhibition of marrow function due to the influenzal infection subsides, the ordinary response to pneumonia can manifest itself.

Measles.—Anæmia does not occur except, in a very slight degree, during convalescence.

Leucocytosis occurs even during the incubation period. This may be of value in early diagnosis in families of which one member has the disease. The occurrence of fever and the appearance of the exanthem is accompanied by leucopenia, which may have been developing for one or two days previously. The leucopenia persists for about two days,

and then the leucocytes gradually return to normal, or even slightly excessive numbers.

Such complications as broncho-pneumonia and otitis media, even if they occur in the leucopenic stage, are accompanied by leucocytosis, except in rare instances in which the prognosis is extremely grave.

Eosinophiles are increased during the incubation period, but are reduced during the febrile stage.

Relative lymphocytosis is usual in the febrile period, and monocytes are often numerous (10 per cent.). Türk cells are not uncommon.

Meningitis (Cerebrospinal).—Neutrophilic leucocytosis is the invariable rule, and high figures may be reached (*e.g.*, 48,000). If recovery occurs the neutrophiles and the total number of leucocytes fall together, while the lymphocytes rise above normal. It is not uncommon to find the percentage of lymphocytes higher than that of the neutrophiles during convalescence. This is equally true of their absolute numbers. A post-infective eosinophilia also develops in these cases.

No such changes occur in fatal cases, and here the neutrophiles continue to increase at the expense of the lymphocytes, and eosinophiles disappear from the blood.

Identical changes occur in cases due to organisms other than the meningococcus.

Mumps.—No changes are found in the red corpuscles, and the observations of different writers vary very much as to the leucocytic changes. Lehndorff states that slight leucopenia is usual, and Arneth contends that, in spite of this, there is definite shift to the left of the neutrophiles. There seems to be no doubt that a slight and transient leucocytosis occurs at the time of subsidence of the swelling of the parotid.

Pneumonia (Lobar).—Changes in the red corpuscles do not occur during the febrile stage, but a few normoblasts may be found. These appear as a result of the great activity of the

marrow, and not as an effect of compensatory excess of erythropoiesis. Anæmia is common in the post-febrile stage, but is never severe; it quite probably results from toxæmia rather than from loss of blood into the exudate, because this is always only slight.

The leucocytes rise suddenly and considerably at the time of occurrence of the first rigor (20,000 to 30,000), and continue to rise for some days. The size of the leucocytosis does not always bear a direct relation to the extent of lung tissue involved. It seems to be dependent on the intensity of the general infection. It is admitted that, as a rule, the most severe general infections are associated with the involvement of the largest portions of lung, but it is not always the case.

The leucocytosis depends entirely upon increase of neutrophiles, which show well-marked or even extreme shift to the left. Many of the neutrophiles also show a positive glycogen reaction. Myelocytes in small numbers are commonly seen.

Eosinophiles are usually absent, lymphocytes much reduced, and monocytes decreased, but the last-named cells often rise a little before the occurrence of the crisis.

The total number of leucocytes falls suddenly at the time of crisis, but this does not occur if pseudo-crises take place. This is not surprising because, after all, such a phenomenon is only the result of collapse. At the true crisis the total leucocytes may fall to normal or even lower, while the neutrophiles gradually return to normal percentage proportions. Eosinophiles and lymphocytes rise quite rapidly, and post-infective lymphocytosis and eosinophilia are the rule during convalescence.

The occurrence of leucocytosis after the crisis should arouse suspicion of the development of some such complication as empyema.

Rheumatism.—In acute rheumatism there is slight leucocytosis (probably never above 15,000 per cubic milli-

metre). This increase of leucocytes often does not reappear if slight relapses take place.

Eosinophiles are decreased at the very beginning of the disease, but return to normal and persist throughout; they are definitely increased during convalescence.

The number of platelets is invariably increased during the febrile period.

Anæmia always develops from the beginning of the disease, and often progresses after the fever has subsided, so that a comparatively severe anæmia may be present during convalescence; but the great pallor of these patients may be very misleading if it be used as a gauge of the degree of anæmia, which is usually much less than would be expected on clinical grounds alone.

Bosc and Carrieu state that increase of monocytes is invariable, even in those cases in which slight increase of neutrophiles is present. Myelocytes are found, in small numbers, in a relatively large proportion of cases. These writers describe peculiar inclusions in the cells of the joint fluid in acute rheumatism. These bodies stain only with Giemsa, and are dust-like or coccoid particles. Bosc states that identical structures can also be found in some of the circulating monocytes.

Chronic Rheumatism is so very vague a clinical conception that statements as to the blood changes accompanying it are of little value, but, in those cases commonly known as chronic rheumatism a definite lymphocytosis is practically invariably present.

Chronic Muscular Rheumatism (**Fibrositis**) does, however, present some interesting changes in the blood. Bittorf was the first to point out that eosinophilia was always present in the acute stages, and even during relapses; it disappears with subsidence of the symptoms. In very mild acute cases there is also a slight monocytosis. These changes do not occur in chronic forms of muscular rheumatism, and, therefore, it is very doubtful whether Bittorf's explanation

that the eosinophilia depends upon altered muscular metabolism can be accepted. Synwoldt has recorded similar changes, as has also Staeckert.

There are, however, a number of writers (Kaufmann, Stückgold), who have been unable to confirm these observations. It seems possible that two different pathological processes have been included under the same name, and that this is the explanation of the divergent findings.

It seems to be certain that *acute polymyositis* is always accompanied by eosinophilia, which may reach a very intense degree (Dragoewa), but it persists only for a day or two. This is a valuable differential feature between acute polymyositis and infestation with Trichina spiralis, which causes persistent eosinophilia.

Rubella.—Slight leucopenia or, less commonly, a normal number of leucocytes is found in German measles. The lowest number is seen on the third day after the appearance of the rash, but the neutrophiles reach their lowest level on the sixth or seventh day. The fall of neutrophiles is accompanied by an increase of all the normal mono-nuclear cells, *i.e.*, both lymphocytes and monocytes.

The most interesting change in the composition of the blood is found in the high percentage of plasma cells and Türk cells (Hickling); these reach numbers much higher than are found in any other infective disease. This occurrence may be of very great diagnostic importance in distinguishing rubella from scarlatina or measles.

Scarlatina.—Some anæmia always occurs, but, even in very severe cases, is only slight; nevertheless, it is common to find a few erythroblasts in the blood.

Leucocytosis commences even before the appearance of the rash, and runs a course parallel to the temperature. Neutrophilia is the characteristic feature of the leucocytosis, which reaches very high figures, *e.g.*, 50,000 per cubic millimetre. Myelocytes are almost invariably present, even when the degree of shift to the left of the neutrophiles is otherwise

not very extreme. The leucocytosis often persists after the fever has disappeared, and may even increase. Fall of the leucocytes occurs at the same time as the beginning of desquamation.

The most striking feature of the leucocyte count is the high percentage of eosinophiles (25 per cent. in one case recorded by Naegeli). It is very important to realise that scarlet fever is the only acute infective fever in which eosinophilia occurs. It has already been mentioned that practically all neutrophilic leucocytoses of infective origin are associated with eosinopenia, or even total absence, of these cells from the blood. In fatal cases of scarlatina eosinopenia always occurs, as it does also if complications ensue. The number of eosinophiles decreases as the disease progresses, but a post-infective eosinophilia occurs, just as in the case of other infections.

During the acute stage of the disease, the lymphocytes are very much reduced, but they gradually return to normal numbers, and then rise to figures much above those of health (post-infective lymphocytosis).

Türk cells are usually present in small percentage numbers.

Another interesting observation on the blood picture of scarlatina is that of Döhle, who described the occurrence of certain small inclusion bodies in the neutrophilic leucocytes in this disease. There is nothing to support the view of some writers that these "Döhle bodies" are spirochætes; it appears certain that they represent degenerations of the cytoplasm. Further, although they are most commonly found in the neutrophiles of scarlatina, they are not uncommon in other infective maladies. According to Hirschfeld they may, as a great rarity, be found in normal blood.

Syphilis.—In the primary stage anæmia is never at all well marked. The pallor is the result of vaso-motor disturbance, but Fischer and Chen Pan Nien state that definite reduction of both hæmoglobin and red corpuscles may occur.

In the secondary stage anæmia is never severe, but is

rather more common than in association with the primary manifestations.

In the tertiary stage anæmia is commoner, but is not severe, although Winterfeld has described a case in which the red corpuscles fell to 1,200,000 per cubic millimetre.

It is admitted by a very large number of hæmatologists that a blood picture identical with that of pernicious anæmia may occur as a result of syphilitic infection. Many writers go so far as to maintain that syphilis is one of the causes of this disease. This view has already been supported in this book, in spite of the criticisms of Winterfeld.

Variations in the number of leucocytes are very different in different cases. Kyrle has investigated 100 early cases, and finds that, in about equal numbers, there are syphilitics with a normal number of leucocytes, with slight leucocytosis, and with well-marked leucocytosis. He could find no relationship between the severity of the infection and the characters of the leucocytic blood picture, nor between the extent of cutaneous manifestations of the disease and the blood. Cases with low numbers of leucocytes showed no alteration in the numbers as the result of treatment, but those with definite leucocytosis showed an immediate fall to about normal. There can thus be little doubt that the leucocytosis was the result of the syphilitic infection.

It must not be forgotten that, fortunately rarely, aplastic anæmia (myelophthisis) may develop after treatment with salvarsan. Less severe manifestations of marrow injury, such as thrombocytopenia with tendency to spontaneous hæmorrhages may also rarely occur from the same cause.

In cases of congenital syphilis the blood picture may resemble that of anæmia pseudo-leukæmica infantum (p. 243).

The question of the relationship of syphilitic infection to " blood diseases " as a whole has often been discussed, but with very discordant results. Some reference here is probably essential, although the whole subject is extremely obscure.

Hoff has investigated the matter in some detail, and is of opinion that relationships between syphilis and a variety of "blood diseases" are of more importance than is usually supposed to be the case.

Severe anæmias occur practically only in the tertiary stage, and, as Hoppe-Seyler has pointed out, are often associated with syphilitic involvement of the liver. For example, a man with hepatic syphilis showed 2,600,000 red corpuscles and 2,000 leucocytes per cubic millimetre, but, after a month of anti-syphilitic treatment, the anæmia disappeared and the leucocytes returned to normal numbers. He was still in good health and showed no sign of anæmia.

That severe anæmia can occur in infants as the result of syphilis with no admixture of mal-nutrition or rickets is shown by a case recorded by Hoff :—

A child, aged one month, had positive Wassermann reaction, macular eruption, paronychiæ, and splenomegaly. The blood showed 2,740,000 red corpuscles and 23,600 leucocytes per cubic millimetre. Myeloblasts and myelocytes were present, and the picture was that of von Jaksch's anæmia. Only 75,300 blood platelets were present per cubic millimetre. Death occurred at the age of three months.

There would seem to be but little doubt that this is an example of severe anæmia entirely due to congenital syphilis.

One of the most interesting questions is the frequency of syphilis in sufferers from pernicious anæmia ; it has already been mentioned that syphilis may rarely be the cause of a condition with all the typical signs of pernicious anæmia, but that is not quite the point at issue here. Hoff states that he has seen ten cases of syphilis associated with pernicious anæmia, but it is, of course, possible that this is nothing more than coincidence. He does, however, adduce some evidence that this is not the case. Wolff, basing his conclusions on 2,180 autopsies, states that syphilitic aortitis occurred in 6·8 per cent. of the cases, and Oberndorfer

gives an almost identical figure derived from 1,364 post-mortem examinations. These are higher figures than are usually stated, *e.g.*, Gruber saw syphilitic aortitis in only 4 per cent. of bodies in 6,189 autopsies. Now, Hoff states that, in twenty-four cases of pernicious anæmia, syphilitic aortitis was found in ten bodies at autopsy. He admits that the number of cases is too small to form the basis of any far-reaching conclusion, but it certainly does seem to be highly probable that syphilis is commoner in the sufferers from pernicious anæmia than in the general population.

Further, Hoff states that he has found the Wassermann reaction far from satisfactory in pernicious anæmia; in five of his syphilitic cases it was negative, and in fact it was strongly positive in only one of the series. This is the more striking when it is recollected that, in cases of aortitis, Wolff found a positive reaction in 80·9 per cent.

It is obviously not justifiable to pay too much attention to these observations, but it is well to realise that syphilitic infection does result in changes in the red corpuscles, and could, therefore, well act as one of the noxious stimuli capable of causing pernicious anæmia.

Descriptions of the effects of *congenital syphilis* on the blood are rather divergent, but it is usually admitted that important alterations may occur. Zanca, in a study based on forty-five cases, reaches conclusions which seem to be of general value. He states that the hæmoglobin index is almost always either below or above normal, although the former is the more usual. The red corpuscles are practically invariably reduced, and leucocytosis is the rule. The increase of leucocytes depends upon a well-marked lymphocytosis, but immature myeloid cells are quite often seen.

He arranges the cases in two distinct groups :—

(*a*) Simple anæmia in which the number of red cells does not fall below two millions per cubic millimetre ; and

(*b*) Severe anæmia, in which the red corpuscles are usually below this number.

The severe anæmias of congenital syphilis are subdivided into two classes :—

1. Anæmia of "pernicious" type, and
2. Pseudo-leukæmic anæmia (see p. 243).

Four varieties of the "pernicious" type of congenital syphilitic anæmia are described :—

A. Of orthoplastic form, *i.e.*, with a normoblastic type of blood regeneration and ordinary myeloid reaction.

B. Of metaplastic form, *i.e.*, with embryonic myeloid reaction.

C. Of hypoplastic form, *i.e.*, characterised by evidence, in the blood, of defective reaction in the bone marrow, and

D. Of aplastic form, *i.e.*, with failure of myeloid reaction. This type is extremely rare.

The pseudo-leukæmic form of congenital syphilitic anæmia also manifests itself in four forms :—

A. Myeloid type in which neutrophilic polymorphonuclear leucocytosis and a small percentage of myelocytes characterises the blood picture. This is the commonest form.

B. Lymphatic type in which lymphocytes are predominant in the blood.

C. Mixed type, in which both lymphocytes and granulocytes are present in excess ; and

D. Eosinophilic form, which is rare, and is accompanied by great increase of eosinophiles.

Tetanus.—There are no very notable changes in the blood in this disease, but slight leucocytosis may be present. This may be either decreased or increased after injection of anti-tetanic serum. Extreme leucocytosis occurs during the spasms. Undoubtedly this is due entirely to the violent muscular contractions, *i.e.*, it is not a real myelogenous leucocytosis, but a myogenic one. It is quite probable that all the changes in the blood in tetanus are entirely the result of the convulsions.

Tuberculosis.—In the early stages of tuberculosis it is common to find a definite anæmia with low colour index.

This has frequently been mistaken for chlorosis in young girls. At the stage of the disease in which cachexia is commencing it is usual to find normal numbers of red corpuscles and normal amount of hæmoglobin. There is but little doubt that this is due to concentration of the plasma, *i.e.*, that there is really an anæmia present in spite of the morphological appearances. Even a slight polycythæmia, doubtless of similar origin, may be found at this time.

Severe hæmoptysis and also secondary infections tend to induce anæmia in the later stages of pulmonary tuberculosis.

Lymphocytosis is present in the early stages of cases with good prognosis (Steffen). The absence of lymphocytosis, the presence of neutrophilia and the occurrence of leucocytosis, are all bad signs. It must be emphasised that the early lymphocytosis of cases with good prognosis may occasionally be an absolute one, associated with a relative decrease in number. There can be no doubt that well-marked and progressive shift to the left of the neutrophiles is never of good significance, but too much stress must not be laid on the neutrophilic blood picture, although intense nuclear shift must always arouse suspicion of secondary infection.

Glandular tuberculosis, if not extensive, is not accompanied by changes in the blood, but widespread destruction of lymphatic tissue is, of course, associated with lymphocytopenia.

Miliary tuberculosis is accompanied by relative or absolute neutrophilia, but the number of leucocytes may be reduced, normal or increased. Eosinophiles are always scanty.

Typhoid Fever.—Anæmia practically always develops, probably as the result of the length of the illness and the poverty of the diet.

The characteristic feature of the blood picture is a very definite leucopenia, which occurs immediately after a very transient initial leucocytosis. Return to normal numbers of leucocytes occurs only at the onset of convalescence, unless complications intervene.

The neutrophiles rise very slightly for a very short time, and then, within the first week, start to fall until the beginning of convalescence, when they begin to rise.

The lymphocytes fall during the short period of leucocytosis and neutrophilia, but then gradually increase to numbers greater than those of the neutrophiles ; the crossing of the lines indicating neutrophiles and lymphocytes respectively usually takes place towards the end of the third week of the disease. Post-infective lymphocytosis persists for a considerable time during convalescence.

The monocytes increase and decrease parallel to the neutrophiles.

It is not uncommon to find leucopenia and decrease of eosinophiles persisting for some months after prophylactic injection of typhoid vaccines ; this must make for caution in the hæmatological diagnosis of typhoid fever. It is interesting to compare the effects of a single injection of typhoid vaccine on the blood with the appearances seen in early typhoid fever ; in both cases there is a transient leucocytosis, which is followed by leucopenia. In the case of a single injection of typhoid vaccine the leucocytosis persists for five or six days.

Paratyphoid Fever is not so invariably accompanied by leucopenia, although this is the rule. Eosinophilia of considerable degree is said to be comparatively common (Marcovici), but by the ninth or tenth day of the disease monocytosis is quite common (Piney and Berrie) ; this statement applies also to infections with B. Gaertner.

Typhus.—Anæmia practically always develops, and, according to Wolff, may show a colour index above unity, but this appears to be an isolated observation of this occurrence.

Leucopenia certainly occurs before the appearance of the eruption (Marcovici) ; then a very definite leucocytosis develops (Schilling). The neutrophilia persists until convalescence is well established, and then gradually a normal

blood picture reappears. Definite shift to the left of the neutrophiles, with appearance in the blood of band and young forms, is invariably found, and even myelocytes may be present.

Tuschinsky has recorded monocytosis at the acme of the fever, and also during its fall. He further calls attention to the possibility of finding endothelial cells in the blood if the ear be well rubbed before blood is taken (cf. endocarditis lenta).

Varicella.—Leucocytosis occasionally occurs, but the numbers are usually normal. Shift to the left is always present, and recovery is accompanied by post-infective increase of eosinophiles and plasma cells.

Vaccination is followed by slight leucocytosis, which passes to normal at the time that the local reactions have reached their maximum. The leucocytes rise again, but only slightly, within the next few days. The first leucocytosis depends upon neutrophilia, and the second upon lymphocytosis. Eosinophilia often occurs after the other blood changes have disappeared.

Variola.—Anæmia of considerable severity may develop in the more protracted cases, but usually becomes marked only in the post-febrile stage. Erythroblasts and polychromasic red corpuscles are quite commonly found, even before the occurrence of anæmia ; this must be the result of irritation of the bone marrow, which is also demonstrated by the leucocytic changes.

Extreme degrees of leucocytosis are quite usual, particularly in the pustular stage in which 40,000 or even more leucocytes may be present per cubic millimetre. Schilling has emphasised the occurrence of a very intense shift to the left of the neutrophiles ; this is so great that a considerable percentage of myelocytes is usually found. Although the nuclear shift is so great, there is no relative neutrophilia ; numbers of neutrophiles above 50 per cent. are quite uncommon. Quite early in the disease monocytosis occurs,

and monocytes may form as much as 50 per cent. of the total leucocytes.

Eosinophiles are much reduced, but are rarely quite absent. Türk cells are always present in relatively large numbers.

As in the case of other infections, very severe forms of the disease are accompanied by leucopenia.

The monocytosis can be regarded as additional evidence of the widespread injury to endothelium, which has been discussed in Chapter IX. in the section dealing with purpura variolosa.

Whooping Cough.—Leucocytosis is always present from the catarrhal stage onwards; in some cases, probably the majority, this results from the presence of a lymphocytosis, but in others neutrophilia is present.

Schneider is the author of most of our accurate knowledge of the blood picture in whooping cough; he states that leucocytosis is invariable, and starts rapidly at the onset of the catarrhal stage. Numbers as high as 39,000 per cubic millimetre were found even in uncomplicated cases; and the lymphocytosis, which is usually between 58 and 63 per cent., may rise as high as 86 per cent. Monocytes vary only slightly, but tend to be a little above normal numbers.

There are a few *tropical diseases* in which the characters of the blood picture are fairly well known, but it can be said that these maladies have almost all been insufficiently investigated.

Beri-beri.—There is always some anæmia, which may become severe.

There is little change in the number of leucocytes, but slight transient lymphocytosis is common.

Cholera.—Blood changes in this disease result both from toxic action and from increased viscosity due to copious diarrhœa. Benzler has shown that there is definite monocytosis during the prodromal period, and this is replaced by neutrophilia with shift to the left at the onset of the initial

diarrhœa; this is accompanied by lymphocytopenia and monocytopenia. The real onset of the disease is accompanied by a great neutrophilic leucocytosis and shift to the left, intense lymphocytopenia, and slight monocytosis; Türk cells also always appear in the blood. Monocytosis increases markedly during the algid stage, but is replaced by lymphocytosis in the reactive stage, and this persists into convalescence.

Dysentery (Amœbic).—Anæmia, as is well known, may be extreme in severe cases. Leucocytosis and eosinophilia are usual, but the latter is by no means invariable; in any cases the eosinophiles fall or even disappear if a liver abscess develops.

Malaria.—Anæmia may, of course, develop and become severe.

Neutrophilia, both relative and absolute, with marked shift to the left occurs during the rigor. Leucopenia with neutropenia is usual at the acme of the fever, and is invariable after it, when the monocytes increase. Monocytosis of considerable intensity is usual in relapsing or chronic cases; it is, of course, to be remembered that particles of black malarial pigment are commonly found in these cells.

Sprue.—The blood changes in this disease are of interest, because it is stated that, in rare instances, they may be identical with those of pernicious anæmia, although, of course, recovery may take place.

The condition of the blood in association with **Disorders of Endocrine Glands** does not present much of interest, which is surprising when it is recollected that the normal emigration of cells from the hæmatopoietic tissues is probably due to a chemical correlation, rather than to nervous action.

Adrenals.—No very characteristic changes occur, but severe anæmia is quite common, and leucocytosis is not rare.

Tumours of the adrenals associated with alterations of secondary sexual characters usually present a blood picture very like that of Hodgkin's disease (p. 143).

Pituitary.—No notable changes are known, but lymphocytosis of slight degree is common.

Thyroid.—No changes of sufficient intensity to be of clinical value are known, and the various records are very divergent.

Spleen.—It is, of course, not certain that the spleen is to be regarded as being an organ of internal secretion, but there is no doubt that it has some regulatory function on myeloid tissue; this is well shown by the alterations in the blood picture after splenectomy (p. 91). Schilling records a case in which a persistence of Jolly bodies in the red corpuscles of a patient led him to presume the presence of splenic atrophy, and autopsy confirmed his diagnosis, *i.e.*, the effect of the atrophy was similar to, but less intense than that due to splenectomy.

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CHAPTER XI

SPLENOMEGALY

I. Gaucher's Disease and Allied Conditions

The term splenomegaly, of course, implies nothing more than enlargement of the spleen, and a number of such conditions, of unknown or uncertain ætiology, require discussion.

Gaucher's Disease, in spite of its rarity, is of such great interest and theoretical importance that some further description is essential.

The disease is sometimes familial in its incidence, but isolated cases are quite commonly found.

The clinical course, if death does not occur in infancy, is extremely slow, and the malady is usually detected in the course of an examination for some other reason. Both the spleen and the liver are enlarged, but the latter to a much less degree. Although extreme chronicity is the rule, some cases progress in more acute intermittent stages (Rusca), but the average length of life after the diagnosis is made is about twenty years. Symptoms referable to the large size of the spleen naturally occur, and interference with the left kidney may even result in hydronephrosis (Mienzil).

The superficial lymphatic glands are practically never enlarged. Bone pains (dolores osteocopi of Rusca) are not rare in the later stages of the disease ; and muscular pains, particularly in the calves, occur at the same time.

A slightly jaundiced or brownish colour of the skin develops quite early ; it is most marked on surfaces exposed to light, and does not involve the mucosæ.

It is common, but by no means invariable to find a

brownish pinguecula on the conjunctivæ ; this usually starts on the nasal side.

Leucopenia, either neutropenia or lymphocytopenia, occurs quite early, but anæmia is very slight for long periods of time. Thrombocytopenia is practically invariable (Lippmann, Zadek), but is not sufficiently intense to result in the development of a hæmorrhagic diathesis in the ordinary sense of the word, although these persons usually bruise unduly readily.

Clinical diagnosis is usually not possible, but may become so if splenic puncture is performed (Reuben), as the typical Gaucher cells can be found in the material stuck in the lumen of the needle.

The so-called Gaucher cells, which are so characteristic of the histological picture, require some description.

Their cytoplasm, which looks structureless in fresh preparations, is seen, in fixed tissues, to be filled with very fine fibrils, which tend to have a longitudinal arrangement. Hyaline droplets are not uncommonly seen between the fibrils, or even between the cells (Foot and Ladd). Evans states that the Gaucher cell does not possess mitochondria. The cells contain one or more nuclei according to their size ; and large syncytial masses with numerous nuclei are quite common.

In the spleen, the cells tend to present an alveolar arrangement ; adjacent acini may fuse together and so present the appearance of larger cell masses. Each mass is surrounded by a finely fibrillar capsule in which a few curved, narrow " endothelial " cells may be present. In many of the masses it is easy to find that a small arteriole lies in the midst of the cells (Pick) ; the cells also surround the sinuses, but the former appearance is the one from which one is more entitled to infer that the Gaucher cells are modifications of the adventitial cells. The Malpighian bodies may be reduced in number, but in all cases are decreased in size ; presumably, as the result of compression. The trabeculæ may be increased in size, but small hæmorrhages are always seen in

their substance; similar bleeding may occur round the Malpighian bodies (Evans).

Hæmosiderin is always present, except in the very earliest infantile cases; it is found inside the cells of the sinuses as well as in the real Gaucher cells themselves. It is usual to find that not all the pigment gives the reaction of free iron, and its nature is, as yet, undetermined. It is commoner to find a diffuse staining of the Gaucher cells with the reagents used for the demonstration of iron than to see particles of pigment in them.

It is not common to find evidence of erythrophagocytosis on the part of the Gaucher cells (Kraus), but it does occur.

Small collections of myeloid leucocytes and megakaryocytes are quite commonly present between the Gaucher cells (Waugh and MacIntosh); these myeloid metaplastic patches contain myelocytes, but myeloblasts are rare.

Cysts of various sizes are quite commonly found in the spleen; and these are lined either by "endothelial" cells or by fibrillar connective tissue, which may form septa dividing the cavity into spaces. The cysts, which are visible only microscopically, appear to be derived from vascular dilatation; in some cases, such enlargements may become macroscopically appreciable. Myelopoiesis is very commonly distinguishable in these dilated blood channels.

It is common to find areas of necrosis which may be minute or may reach considerable proportions; these arise by simple death of the cells and their replacement by scar tissue, which is often infiltrated with pigment.

In the liver, there is usually a diffuse cirrhosis which is not often associated with proliferation of the bile ducts, although this may occur (Kraus). Particularly in infants, all signs of hepatic cirrhosis may be absent. Gaucher cells are present both in the lumina of the capillaries and in the adventitia of the central lobular vein. The cirrhosis is never a simple increase of fibrous tissue, but is always accompanied

by the presence of Gaucher cells in the connective tissue; they may be isolated or may form small agglomerations which are surrounded and penetrated by very fine argentophilic fibrils. It is very striking that the Gaucher cells in the liver tend to be more elongated in shape than do those in the spleen, and they also show fusion, with consequent formation of long syncytial masses. They tend to infiltrate the branches of the portal vein and penetrate the tunica media, but may even reach the lumen (Mandlebaum and Downey).

Superficial lymphatic glands are very rarely involved, but mesenteric ones frequently show infiltration with Gaucher cells, which ultimately so compress the normal components as to cause atrophy. Pigmentation is usually very well marked, and is often more intense than that in the spleen and liver, but it is quite common to find the most marked pigmentation in glands in which the number of Gaucher cells is small. It is very striking to observe, in early cases, that the first appearance of Gaucher cells is found in the " germ centres " of the gland (Evans).

The intensity of the affection of the bone marrow bears no necessary relation to the duration of the disease, and extensive involvement of the skeleton has been found even in infants (Kraus). The infiltrations of Gaucher cells in the marrow may consist of isolated cells or of larger groups, but in any case they are much less well demarcated from the myeloid tissue than they are from the lymphatic cells in spleen and glands. Gaucher cells in the marrow may have the typical polyhedral form, which is characteristic in spleen tissue, but many of them are elongated and show longitudinal fibrillation very distinctly. Fine fibrils are numerous between the cells, and many of them seem to fuse with (or be derived from) the edge of the protoplasm of the Gaucher cells. Gradual atrophy of the cells and replacement by fibrillar scar tissue occurs in the same way as in the spleen and liver, and at the same time infiltration with pigment occurs.

There are a number of publications in which Gaucher cells are recorded as occurring in other organs. Risel mentions the presence of a small mass of these cells in the thyroid, where they probably arose in a misplaced portion of lymphatic tissue. In infants it is common to find the thymus replaced by large cells which are usually regarded as being identical with Gaucher cells (Rusca), but it has to be remembered that it is common to find swelling of thymic reticulum cells, due to infiltration with lipoids and even hæmosiderin, as a result of various infections (Lubarsch). A similar objection holds in the case of descriptions of Gaucher cells in intestinal lymphatic follicles (Evans).

Very little is known about the *chemical nature* of the substance contained in the swollen cells of Gaucher's disease, but a few observations deserve reference. No method of staining of either fresh or fixed material has demonstrated any chemical reaction of known meaning in these cells. The resemblance of the cells to those seen in " xanthomata " has naturally suggested that the substance might be of ordinary lipoidal nature, but no demonstration has shown this; and Mandlebaum very rightly says that any case of large-celled infiltration of the spleen in which lipoids can be demonstrated is not Gaucher's disease.

Millon's reagent and the xanthoproteic test both give weakly positive results; and the substance of the Gaucher cells is digested both by pepsin and trypsin. Risel has, therefore, supposed that some unknown protein substance is present. Pick points out that with Mallory's triple stain there is a marked resemblance between the reaction of the Gaucher substance and that of amyloid; this is yet another evidence of the protein nature of the material.

Negative results in staining for lipoids have to be judged cautiously, because as Kutschera-Aichbergen has shown, not all lipoidal substances are capable of micro-chemical demonstration; in fact he states that while the primarily acetone-soluble lipoids can be stained (cholesterol and cholesterol

esters), the primarily alcohol-soluble ones cannot be demonstrated (lecithin, etc.).

General chemical investigations of the composition of normal and Gaucher spleens have shown (Epstein) that neither cholesterin nor lecithin form a noteworthy part of Gaucher spleens. He showed, however, that the deposit left after evaporation of ethereal extracts was three times more bulky than normal in the case of Gaucher spleens. There must, thus, be present some substance which is soluble in alcohol, but insoluble in ether. Alcoholic extracts contain a precipitable substance which Epstein regards as a sphingogalactoside. Lieb goes so far as to identify this material with kerasin, which is a substance closely allied to cerebrin. Kerasin swells very considerably on the addition of water, and this may, in part, account for the swollen appearance of Gaucher cells ; there can, however, be no doubt that other substances are present in the cytoplasm, and in fact it is probable that the cells in their abnormally active state store foreign substances almost indiscriminately.

The involvement of the spleen is usually the most striking feature of the disease, but there are cases in which the skeleton is the most severely affected part. It is very striking that the tendency to familial incidence is more marked in the skeletal form of Gaucher's disease than in the ordinary type in which splenomegaly dominates the picture. There can be little doubt that we are here faced with two constitutional familial peculiarities, viz., a tendency to the development of Gaucher cells, and a predisposition of the skeleton to attack by the disease. The histological features of the skeletal forms of the malady differ in no essential particular from those in the splenomegalic type, but it is important to realise that there is never any erosion of the overlying compact bone, even in places where it is normally very thin.

Until quite recently there have been two schools of thought regarding the histogenesis of this disease ; it was held by the

one that " endothelial " cells were essentially affected, while the other contended that the site of the lesion was in " reticulum " cells. It is obvious that the conception of the reticulo-endothelial system put an end to such disputes.

Reference has already been made to the great capacity for storing foreign materials possessed by the reticulo-endothelium, *e.g.*, cholesterol, and lipoid-protein mixtures (Chalatow) ; and casein (Kuczynski). The cells storing these substances certainly belong to the reticulo-endothelial system, because Anitschkow has shown that the cells containing the foreign substance can, at the same time, be shown to stain with trypan blue. It is convenient to erect a working hypothesis, and to regard Gaucher's disease as an example of storage of an endogenous substance or substances, either excessively or as a result of elaboration of unusual products of abnormal metabolism. It is clearly demonstrated that the storage of different substances has different effects upon the reticulo-endothelium ; it will be shown later that storage of lipoidal material in cases of diabetic lipoidæmia occurs, but results in much less reactive hyperplasia than is caused by the *Gaucher substance.*

Pick has contended that in the Gaucher spleen, only the " reticulum cells " and not the " endothelial " ones take part in the process of storage of the foreign substance. It has previously been pointed out that the " endothelial " and the " reticular " components of the reticulo-endothelium are essentially one and the same cell. In some circumstances there is much formation of fibrils, while, in others, cells with very little such differentiation predominate. It is, thus, necessary to modify Pick's statement by saying that storage of " Gaucher material " is associated with a tendency to the development of reticular cells by the reticulo-endothelium. This must, of course, not be taken to imply that " endothelial " cells are absent ; they persist and indeed are usually found to be pigmented ; it appears that the Gaucher cells are swollen reticulum cells, which by increase of

their cytoplasmic bulk come closely to resemble their endothelial relatives. These reticulum cells are obviously perivascular in position (clasmatocytes of Ranvier, pericytes of more recent writers); and it seems certain that, in the liver also, it is not the capillary endothelium which produces the Gaucher cells, but the peri-capillary cells, although Bárat has recently regarded the endothelium itself as the source of the essential elements.

It is necessary to refer to Downey's demonstration of the fact that the lining cells of the lymphatic sinuses in lymphatic glands are nothing other than differentiations of the general reticular (histiocytic) framework of the organs. He was able to show that fine fibrils lay inside as well as outside the lining cells. It is from these true reticulo-endothelial elements that the Gaucher cells of lymphatic glands develop. Presumably they do not arise directly from sinus-endothelium in the spleen, because that is a more differentiated tissue than is the corresponding one in glands.

The history of the views as to the pathogenesis of Gaucher's disease includes neoplastic, generalised hæmatopoietic injury and metabolic theories. It is difficult to decide between the claims of the theory that Gaucher's disease is a primary anomaly of metabolism, and the one that it is essentially a disease of the reticulo-endothelial system.

The importance of a constitutional factor in the genesis of the disease is obvious when the familial incidence is remembered; this is supported also by the frequency with which Gaucher's disease is accompanied by other malformations, *e.g.*, patency of the foramen ovale, multiple cysts of the ovaries, horse-shoe kidney, and congenital cysts in the spleen.

The disease can be regarded as being due to excessive storage on the part of the reticulo-endothelium, but it can equally well be considered as being the result of a defective reticulo-endothelial system, which is too poorly developed to be able to metabolise the substances it has ingested.

Epstein prefers to regard the disease as being one due to

interference with metabolism, in which abnormal products circulate and are stored by the reticulo-endothelium in exactly the same way as are various dye-stuffs after experimental injection.

It is not possible to agree with Waugh and MacIntosh in the view that Gaucher's disease is a primary malady of hæmatopoietic tissue of the nature of an aleukæmic dysmyelosis; this explanation takes no account of the almost invariably practically normal blood picture, which is surely incompatible with the activity of an abnormal hæmatopoietic tissue.

It will be convenient to defer the discussion of the ætiological theory, which makes most appeal to the present writer, until one or two other forms of splenomegaly have been described.

First, the so-called "**Niemann's splenomegaly**" needs to be mentioned. The essential features of the malady can best be appreciated from a summary of the findings in a case recorded by Schiff. The patient was a boy, aged seventeen months, who had not thriven at any time since birth. He had had a number of febrile attacks, and, five months before admission, had erysipelas. Swelling of the abdomen had been noticed since the age of three months, and the boy had a very well-marked lingua geographica. The blood showed 4,600,000 red corpuscles per cubic millimetre, and 10,800 leucocytes, of which 49 per cent. were lymphocytes. Schiff particularly remarks on the fact that excess of lipoids in the blood caused turbidity, which persisted even as long as four hours after a meal. Platelets numbered 20,000 per cubic millimetre.

Great swelling of liver and spleen, together with a peculiar discolouration of the skin, completed the clinical picture.

The diagnosis was confirmed by examination of films made from material obtained by splenic puncture.

Only nine certain cases are recorded in the literature, and of these seven were in females: two sisters in one

instance, and probably the same incidence in Siegmund's case, but here one sister died without autopsy being possible.

Most of the cases showed other anomalies associated with the more striking splenomegaly and hepatomegaly, thus Niemann, who recorded the first case, noted that the girl had the appearance of a mongol.

Knox, Wahl and Schmeisser saw the disease in two sisters : Siegmund also saw the same familial incidence ; and Bloom observed the disease in a mongoloid girl, aged sixteen months.

We shall have to refer to the importance of a constitutional factor when the discussion of the ætiology of the disease is undertaken.

The pathological changes in the affected tissues are very striking. The spleen is very greatly enlarged, and, on section, shows small whitish areas of about the size of a split pea.

It is not common for external lymphatic glands to be involved, but it has been described, and, when this is the case, they are almost bright yellow in colour.

The liver, thymus, bone marrow, and adrenal cortex all show extreme yellow colouration. This can be seen to be due to the presence, in all these organs, of large cells in which lipoids and neutral fats can be demonstrated histologically. Similar cells are quite commonly found in small numbers in organs, which show no macroscopical change.

It is not possible to make out any regularity of arrangement of the cells in the spleen : they are widely scattered in the pulp, which may be almost completely atrophied. The " endothelial " cells lining the sinuses are not involved in the process, although it is not uncommon to see that the large cells have broken through them into the lumen of the sinuses. The appearances are such as to leave little doubt that these cells are of " reticular " origin, just as is the case in Gaucher's disease : they are, however, much less actively phagocytic in Niemann's disease, and ingested red corpuscles are rarely found.

In the liver there are similar changes, but the capillary endothelium also gives rise to the large lipoid-containing cells, whereas this is not the case in Gaucher's disease. The fact that such storage can occur in the vascular lining supports the contention previously made that " reticular " and " endothelial " elements are both manifestations of the one tissue : reticulo-endothelium.

The discussion of the genesis of Niemann's disease will be found in the same section as that dealing with the pathogenesis of Gaucher's splenomegaly, but a description of the hyperplasia of lipoid cells in diabetes mellitus must precede this.

It is, of course, well known that disturbances of fat and lipoid metabolism accompany the disorder of carbohydrate metabolism in *diabetes*. It is quite common to find fatty infiltration of the renal and hepatic cells, and, more rarely, yellow tumour-like masses (xanthomata) occur on the skin and internal organs.

In some cases, lipoidæmia may result in the development of large fat-containing cells in the spleen. A considerable number of such cases are on record, but the one published by Schöndorf is particularly illustrative. The pulp of the spleen was practically replaced by large cells, which were mostly arranged in columns and irregular masses, and practically completely replaced the pulp, but left the endothelium of the sinuses intact. Enlargement of the spleen may be present, but is never very striking ; the colour of the organ is almost always altered, and rather resembles milk chocolate in this respect (Schultze).

Organs other than the spleen rarely contain these cells, but they were present, in small numbers, in the femoral marrow, the liver and mesenteric lymphatic glands in a case recorded by Pick. The adrenal cortex is yellower than normal and it is quite common to find small areas of storage of yellow fatty material in the endothelium of the cardiac valves and of the arteries : an appearance, which is very like that seen

in the early stages of atheroma. The changes are very similar to those described by Anitschkow in animals fed on excess of cholesterol, and presumably the genesis is, in both cases, similar.

The material stored in the cells does not give all the histological reactions of fat, and some of it resembles adipose material only inasmuch as it stains with reagents used for the demonstration of myelin ; it is quite common to find that the reactions of the cell contents vary somewhat even in different organs, from the same case ; and it is usual to find that fat-staining is much more obvious in the intra-vascular blood than in the large cells. Such phenomena might be due to intra-cellular conversion of ingested fat into myelins (Lutz), or to a selective storage of material collected from the blood : such selection might well differ in its quality in different organs, and so explain the peculiar findings.

The " lipoid cells " stain diffusely with those reagents commonly employed to demonstrate the presence of iron : and, in this way, resemble the large cells of both Gaucher's and Niemann's disease.

The real difficulty lies in explaining the practically complete absence of " lipoid cells " from all the organs in some cases of lipoidæmic diabetes : it is scarcely justifiable to attribute this entirely to individual peculiarities of the " reticulum " cells.

The question of pathogenesis may now be discussed, although it is freely admitted that there are many flaws in the theories put forward.

There is obviously no doubt that, in diabetic lipoidæmia, there is a metabolic disturbance before there is any sign of formation of the characteristic large cells in the spleen and other organs. There would seem to be but little reason for supposing that a similar sequence of events is not present in Gaucher's disease, and so we can drop the conception of a primary hyper-activity of the reticulo-endothelium as an

explanation. The metabolic abnormality is presumably an in-born error, as is shown by the tendency to familial incidence, but the nature of the anomaly is quite obscure.

We know that the products (or some of the products) of this abnormal metabolism are stored in " reticulum " cells, but we are quite uncertain whether these substances are of endogenous or of exogenous origin.

The high cholesterol content of the blood in association with Niemann's splenomegaly also suggests that a metabolic abnormality precedes the formation of the large cells : and so further increases the impression that Gaucher's disease must arise in a similar manner.

It is quite impossible to regard the storage processes in Niemann's disease as being due to a primary hyperfunction of reticulo-endothelium because there is often excessive storage of the abnormal metabolic products in parenchymatous cells in the liver, etc. This could not occur if the reticulo-endothelium alone were at fault : and it is more rational to suppose that all these cells store more than normal because they are supplied with more material to take up into their cytoplasm.

Lastly, it is essential to realise that lipoid-containing cells may be found in small numbers in the normal spleen, and are quite numerous in many infections. This fact seems to make clear that there are always cells available for dealing with and storing metabolic products ; and, therefore, if storable material is produced by abnormal metabolism, there will be hyperplasia of this cellular system : the reticulo-endothelium. We can probably go no further than to say that storage of different metabolic products can take place in the reticulo-endothelium, which becomes more or less hyperplastic according to the type of material stored in the protoplasm of its cells.

The question of therapeutic measures is obviously not of much importance in Gaucher's disease, which has so very long a course and interferes so little with health. Niemann's

disease is invariably fatal. Diabetic lipoidæmia can only be dealt with by ordinary anti-diabetic measures.

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CHAPTER XII

SPLENOMEGALY

II. Banti's Disease

Banti, in 1894, described the disease, which now bears his name, but many writers seem to be very much averse to admitting the syndrome as a pathological or clinical entity. There is, of course, no doubt that a malady presenting the features described by Banti does occur, but its classification is admittedly a matter of very great difficulty.

Banti, in his original description, states that there are three stages in the development of the disease, viz., (*a*) The first, or anæmic stage, shows itself clinically in the same way as do other anæmias, but epistaxis is more common than in other anæmic conditions.

There is, in this stage, always some anæmia, but it is rarely very severe : a reduction of red corpuscles to three million and hæmoglobin to 50 per cent. is about as great a diminution as is ever encountered.

There is always enlargement of the spleen, and this may be very great ; the surface is smooth and the organ is not tender.

Neither enlargement of lymphatic glands nor of liver is found in this first stage ; and jaundice is never seen.

Examination of stained films reveals little morphological change : there is poikilocytosis and anisocytosis, but normoblasts are not seen, and the leucocytes show no alterations.

(*a*) The duration of the first stage is variable, and may extend from one to three years.

Administration of arsenic in this early stage seems to result in diminution of the size of the spleen, but it is not

possible to determine whether it also delays the occurrence of the second stage; it is, however, certain that it never prevents the appearance of the later symptoms.

(*b*) The second or intermediate stage is characterised by the occurrence of progressive enlargement of the liver, and lasts for twelve to eighteen months.

At the beginning of the intermediate stage, there is a definite decrease in the amount of urine excreted, and the urine gets darker, while its content of urates rises. Urobilin is also present as the malady develops. Jaundice, which is absent in the first stage, always occurs later.

(*c*) The third or ascitic stage develops gradually, and is often ushered in by a decrease in the size of the enlarged liver. This diminution in size progresses rapidly, and the organ, which was previously easily palpable below the ribs, may become hidden behind them.

The quantity of urine progressively diminishes; urobilin becomes more plentiful, but bile pigments are scanty.

Rise of temperature in the evening is very common, but is only slight.

Patients, who reach the third stage of Banti's disease, usually die from the results of the enormous ascites, within about twelve months of the development of the ascitic stage.

The *condition of the blood* requires further description, although no very spectacular changes occur at any stage of the disease. Banti states that, although anæmia is usual, there may occasionally even be increase in the number of red corpuscles. The amount of hæmoglobin is, however, always below normal to such a degree that the colour index is invariably less than unity. Erythroblasts are not found in the blood at any time.

Leucocytosis never occurs, but leucopenia is very usual: this depends upon neutropenia. The lymphocytes are normal in absolute number, but are often relatively increased.

The pathological anatomy and histology of the disease

also require description, and Banti's account is here again followed. The most important lesions are, as would be expected, in the liver and spleen.

In the first stage, the *spleen* shows thickening of the capsule and trabeculæ, but adhesion to adjacent organs is not common. The Malpighian bodies show no consistent change: some appear normal, others are slightly enlarged, while yet others are small. It is quite common to find an excess of fibrous tissue around the central arteriole of the Malpighian bodies; this may be quite narrow or may involve as much as three-quarters of the structure. The newly-formed connective tissue tends to be hyaline rather than fibrillar in structure, and Banti refers to this change as "fibro-adenia." It is usual to find cells lying in clefts in the fibrous tissue: they seem to differ in no way from the cells normal in the Malpighian body, but Banti entitles them "chromoblasts." The more advanced the disease, the larger the number of follicles affected by fibro-adenia, but it is rare to find complete obliteration of follicles in the first stage of the disease.

It is very striking to note that "germ centres" are absent from practically all the follicles, and, indeed, in some Malpighian bodies, the place of the "germ centre" is occupied by a small necrotic mass.

Banti mentions that thrombosis of vessels in the follicles is quite common, and he also describes irregular thickenings of the reticulum.

In the pulp, the venous sinuses are abnormally widely separated from one another, and the lining cells of the sinuses are most extraordinarily distinct, whereas in the normal spleen they are difficult to distinguish from the lymphatic cells themselves. There is also an appearance which must be interpreted as the result of hyperplasia of these lining cells, and, as a result, transverse sections of the sinuses may closely resemble epithelial channels. The reticulum of the pulp also shows irregular thickening and hyaline change.

It is to the whole process of increase of reticulum, both in Malpighian bodies and in the pulp, that the name "fibro-adenia" should be applied.

Banti also lays stress on the frequency with which thickening of the splenic vein occurs; the appearances are those of chronic phlebitis, which may reach the portal vein, but always leaves the mesenteric vein unaltered.

It is also stated that, even in the first stage, some enlargement of the liver may be present at autopsy, but, apart from fatty degeneration, no notable histological changes can be found; certainly nothing suggestive of an early cirrhosis is demonstrable.

The bone marrow at this time always shows hypoplasia.

In the second stage, the spleen shows only the same alterations as in the earlier condition, but the liver is the seat of much more obvious lesions. The surface is usually slightly granular. There is increase in the amount of interlobular connective tissue, which, according to Banti, takes its origin around the terminal branches of the portal vein. No changes can be detected in the bile-ducts.

In the third stage, the liver is small and the irregularity of the surface resembles that seen in atrophic cirrhosis of the ordinary type. Adhesion to neighbouring structures is very usual.

The histological appearances are those of ordinary multilobular cirrhosis, and small round-celled infiltration of the connective tissue is very rarely present. The bile ducts show well-marked proliferation, just as in the ordinary cases of cirrhosis. Many branches of the portal vein show phlebitic changes, which may even result in stenosis. The liver cells are the seat of well-marked fatty degeneration, but siderosis is absent.

The spleen differs little in its histological characters from the first and second stages, but elastic fibres are now mixed with the connective tissue of the fibro-adenatous areas.

Extension of the inflammatory process to the mesenteric

vein is quite common in the third stage, but is never so severe as in the splenic vein itself.

Banti's views of the *ætiology* of the disease described by him can briefly be summarised. He regarded the malady as being an infective one, although all cultural experiments failed. He imagines an infective agent with a special predilection for the spleen, in which it mainly attacks the reticulum, and so gives rise to the characteristic fibro-adenia. He presumes that the noxa reaches the spleen by way of its artery, because the first histological changes, as has already been mentioned, are found in the central arterioles of the Malpighian bodies. The fact that sections of the bone marrow show no defect in the formation of red cells led Banti to suppose that there was interference with emigration of red corpuscles rather than any defect in their production. He attributed this asthenia of the marrow either to some direct splenic influence or to the elaboration of some myeloid poison by the infective agent in the spleen.

The view that the alterations in the spleen represent the essential changes of the disease naturally led Banti to suggest that splenectomy might be a useful therapeutic measure. This need not be discussed further, but here it must be pointed out that the later in the disease the operation is performed the greater is the risk, and the less is the chance of cure.

The suggestion of Gibson that the disease is due to a fungus has not received much acceptance, but is worthy of mention, as it is almost the only positive suggestion available.

It is not to be forgotten that there are many writers who are not prepared to admit the existence of any separate syndrome requiring the name of Banti's disease ; they would regard such cases as being only atypical forms of hepatic cirrhosis.

It is not possible to decide this question in the light of

our present knowledge, and we shall do well to discuss a more definite malady in which some similar characters are present; this is the so-called "*splenic anæmia*," a form of which was first recorded by Griesinger. The first case published dealt with a boy who had had four attacks of severe anæmia in a period of eighteen months. Each attack was accompanied by fever and swelling of the spleen. The fourth bout proved fatal, and it was surprising that the enlarged spleen decreased in size before death. The disease just mentioned differs from one recorded under the same name by Banti; this writer very properly renamed the malady he described "*anæmia splenica delli adulti*," in order to avoid confusion.

This form of splenic anæmia is characterised by progressive and rapid enlargement of the spleen to an extreme degree. Slight anæmia accompanies this splenomegaly for five or eight years, but ultimately a mild hæmorrhagic diathesis develops and the anæmia becomes rather more severe. Poikilocytosis, which is absent in the first stage, now makes its appearance, but erythroblasts are always rare. Leucopenia is well marked, and the leucocytes may fall below 2,000 per cubic millimetre. There is no change in the liver other than fatty degeneration, and, if cirrhosis is present, the case has to be included under the term "Banti's disease," and not as splenic anæmia.

The enlargement of the spleen is very considerable, but the normal shape is preserved. Histologically, there is fibro-adenia around the central arterioles of the Malpighian bodies, but it may spread until the whole follicle is obliterated. Not all the Malpighian bodies are equally affected by the process, and it is common to find a few, in the early stages, in which the only pathological change is the absence of a definite germ centre, which may be replaced by a small necrotic area. Banti is very emphatic that the fibro-adenatous process starts in the very small arterioles of the follicles and spreads inwards to the central one,

i.e., it is not primarily an affection of the adventitia of the central vessels.

The sinuses of the pulp are narrow, and the amount of

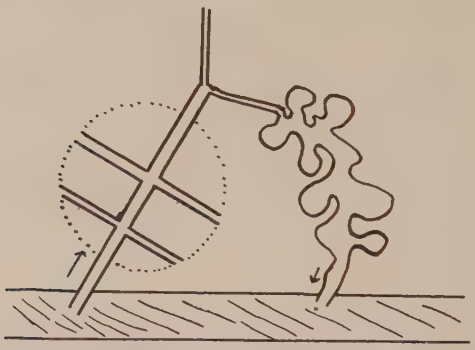

FIG. 18.—Diagram of the course of intra-splenic vessels. (Reprinted from *Brit. Journ. Surgery*, 1926, xiv.)

This is a very simple diagram of the course of a small arteriole and its relation to the sinuses as shown by reconstruction both from injected specimens and from serial sections of well preserved human spleen.

The dotted circle represents the position of the Malpighian body, inside which several lateral branches are given off, and these end in the complex pulp spaces of the spleen from which blood is again collected by venules, but many corpuscles remain in the pulp to undergo destruction by reticulo-endothelial cells. Cells, which escape the lateral paths, pass onwards and reach a trabecular venule after having traversed the sinuses, which are possibly also hæmolytic structures, but are certainly less active in that respect than are the cells lining the pulp spaces.

It is not known what factors influence the passage of cells along either the lateral or the straight channel, but it is probable that even slight differences in size affect the likelihood of one passage or the other; metastases of tumours, which are, of course, rare in the spleen, are found in a more or less ring-like form around the Malpighian bodies, at any rate in their early stages. This fact makes it probable that the larger the elements passing along the arteriole, the greater the chance of their reaching the pulp spaces *vid* the lateral channels. If this is really the correct explanation, it seems possible that the thickening of the walls of the arteriole just beyond the Malpighian body may account, in part, for the excessive hæmolysis of pernicious anæmia in which disease such sclerosis is very common.

pulp is, therefore, increased. There is well-marked increase of large cells with pale nuclei, which resemble epithelium in appearance.

Chronic phlebitis in the splenic vein is usual, and may spread to the portal vein.

Banti has but little to say regarding the ætiology of this disease, but regards it as being due to some infective agent with a special predilection for the spleen. He attributes the anæmia to the action either of an altered splenic metabolism or to some hæmic poison developed by the infective agent. The inflammation of the splenic vein is supposed to be due to the continual flow of such poisons through it.

The theory that the essential primary lesion is in the spleen led Banti to suggest that splenectomy would be the most suitable method of treatment, and it appears that the operation is followed by permanent (?) cure.

No information as to the number of platelets in these cases is available, and it seems to be possible that, as Eppinger suggests, some of them may be forms of " essential thrombocytopenia."

Senator has also described cases of " *splenic anæmia*," but by that term implies something different from both Banti and Griesinger ; it seems that this form of anæmia splenica is really only a name for the early stage of Banti's disease. It must be remembered that Micheli contends that no " splenic anæmia " not terminating in cirrhosis of the liver exists.

Naegeli has put forward the view that splenic anæmia, as a disease sui generis, does not exist ; it is nothing more than a symptom-complex. Many other writers, particularly Türk, have agreed with this view, which is almost certainly correct. There still, however, persists the difficulty that, in the majority of cases which used to be called splenic anæmia, the nature of the malady cannot be discovered.

It has probably already been realised that the clinical picture of " splenic anæmia " is a somewhat variable one, while the pathological changes are much the same in all the cases ; but, of course, there are many cases of anæmia associated with splenomegaly in which an ætiological factor

can be discovered, *e.g.*, malaria. It was never customary to include such cases of known origin in the term "splenic anæmia," and it may well be supposed that with advance of knowledge all need for such an "omnibus" term as splenic anæmia will pass away. Until that time comes, however, it is necessary to refer to *yet another form of anæmia accompanied by enlargement of the spleen.* This type of disease was also described by Banti (1913). The patient was a woman, aged forty-one years, who had borne eight children and had once had malaria. She became gradually anæmic, and is stated to have had definite enlargement of the spleen some two and a half years before she came under Banti's observation. The patient again became pregnant, and her anæmia became worse; after parturition it became really severe and was accompanied by slight jaundice. The spleen was very large and the liver was easily palpable. The blood showed marked hypochromia, poikilocytosis, and anisocytosis. No polychromasia, punctate basophilia or reticulated red corpuscles were found. No alteration in the resistance of the corpuscles to hypotonic saline could be found.

Slight leucopenia was persistently present.

Splenectomy was performed, and the red corpuscles rose to over five millions (from under three millions) in two weeks, but fell again to $3\frac{3}{4}$ millions in a few months. Normoblasts were numerous in the blood for a short time after the operation, but soon disappeared.

Banti supposes that the condition is one of hypofunction of the bone marrow (anhæmatopoiesis). Complete recovery occurred, although severe post-operative pneumonia had interfered with convalescence. Jaundice and urobilinuria, which had been well marked before operation, disappeared, but for a time there were mild exacerbations of both these conditions.

The description of the histological changes states that the Malpighian bodies appeared normal; the pulp was extremely vascular, and many of the cells of its reticulum

were enlarged, as were also those of the venous sinuses. Fragmentation and phagocytosis of red corpuscles were well seen in the pulp spaces, but the reticular fibrils showed no notable changes.

As will be appreciated later, there is good reason for regarding this case as being closely related to, if not identical with, acquired hæmolytic icterus. There is, of course, one great difference, viz., the absence of alteration in the resistance of the corpuscles to hypotonic saline, and it is convenient to retain Banti's name, "*splenomegalia hæmolytica*," until we are in a position to understand the condition more completely.

It is perhaps well to make reference to a case of "*splenic anæmia*" *described by Isaac* in 1912.

A man, of eighteen years of age, was known to have had a large spleen for at least eleven years, and had always been pale and delicate. The enlarged spleen was not tender, and the liver was not palpable. The red corpuscles numbered about three million per cubic millimetre, and the leucocytes 1,800 per cubic millimetre.

The histological changes in the spleen were as follows: Thickening of the capsule and of some of the trabeculæ. The whole of the normal arrangement of splenic tissue had disappeared, and no single Malpighian body could be recognised. The tissue was all very cellular, hæmorrhages were present, and the sinuses were so much compressed as to be very difficult to recognise. A large number of spindle-shaped cells, running in various directions, were present in addition to certain large cells with non-granular protoplasm and round, bent or double nucleus. Macrophages containing red corpuscles were present, but were not numerous.

The liver showed no histological abnormalities.

The bone-marrow was not notably hyperplastic, but the majority of its cells were myeloblasts: this may, of course, have resulted from the terminal septic infection from which the man died.

The appearances differ from any other form of splenomegaly except that following cirrhosis of the liver, but, as that was not present, we are left entirely in the dark as to the nature of the malady.

There is a most important form of *splenomegaly, which was described by Gamna*, and of which little is known, but it presents many features of considerable pathological interest; its rarity is probably due rather to failure to recognise the disease than to infrequency of occurrence.

Gamna states that the changes in this disease differ from those of any other known form of splenomegaly. The clinical course is characterised simply by slowly progressive enlargement of the spleen, unaccompanied by any other disability except a slight anæmia, which becomes severe only towards the end of life. He was not able to find any ætiological factor, but neither syphilis nor malaria seem to be of importance.

There is definite thickening of the splenic capsule, which is adherent to the surrounding structures. Macroscopically the cut section of the spleen reveals the presence of small brownish areas, which are usually surrounded by a hæmorrhagic zone. The essential histological change is a sort of granulomatosis of the pulp, accompanied by atrophy of the follicles. Much ferruginous pigment is deposited in the polymorphous tissue of the pulp, and this is followed by a sclerosis of the new tissue, which ultimately becomes hyaline in appearance until a real hyaline atrophy ensues. The reticular fibrils become fragmented, and so are reduced to structureless debris.

Two cases formed the basis of Gamna's first publication, but he has pursued the subject further in a second paper, in which he for the first time makes use of the name *splenogranulomatosis siderotica*.

Pinoy has made observations on this strange form of splenomegaly, and was able to find bacteria of various shapes in the pulp; there were cocci, diplococci, bacilli, strepto-

bacilli, cysts, and pseudo-mycelial refractile strands. He states that transitions between all these forms can be made out; further, he contends that this disease is relatively common in Algeria. He is of opinion that it is possible that more than this one form of splenomegaly may be due to this organism. Some support is given to the conception of an infective origin of these cases by Pinoy's observation that injection of an organism obtained from three cases of splenomegaly—Synbacterium splenomegaliæ—would reproduce the histological changes in the spleen of the guinea-pig.

It will be obvious that no very definite opinions can be held with regard to "splenic anæmia," and, indeed, it seems highly probable that it will ultimately be possible to dispense with this term completely.

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CHAPTER XIII

SPLENOMEGALY

III. Acholuric Jaundice

The credit for describing this disease is usually, and very justly, given to Minkowski, who read the first report to the "Kongress für innere Medizin," at Wiesbaden, in 1900. He described the occurrence of the malady in eight members of a family in three generations. In each case there was great enlargement of the spleen, icteric colour of the skin and scleræ, the fæces were dark, and the urine, although containing urobilin, was free from bile pigments. The disease appeared to be hereditary and interfered very little with the comfort of the patients, who might reach a good old age.

In one patient, who died of intercurrent infection, there were no changes in the liver; the splenic pulp was congested and hyperplastic, and localised collections of ferruginous pigment were found in the kidneys.

Chauffard was the first to make use of Hamburger's method of investigating the resistance of red corpuscles to hypotonic saline solutions in this disease, and was able to show that, in addition to the slight anæmia, there was a definite increase of the fragility of the red corpuscles in cases of familial acholuric jaundice. Further, he noticed that well-marked microcytosis was very characteristic of the blood picture. He therefore regarded the disease as being due to an inherited abnormality of the red corpuscles, which manifested itself in microcytosis and undue fragility. The jaundice would, in such circumstances, be due to excessive destruction of the abnormal corpuscles in the spleen and liver.

Chauffard, in conjunction with Fiessinger, was able to support this view by demonstrating that hyperfunction of myeloid tissue is invariable; this is shown by the presence of numerous reticulated red corpuscles in the blood, and also of normoblasts.

There are also cases of this disease in which all the typical features are present with the exception of the familial incidence; there is no reason for supposing that these sporadic cases of "hereditary" acholuric jaundice differ essentially from the familial ones.

It is more difficult to decide on the proper classification of similar cases which first manifest themselves in later life (Hayem and Widal), without any evidence of inheritance or of familial incidence.

It will be most convenient to discuss individual features of the disease separately.

The *anæmia* is practically never severe; reduction of hæmoglobin below 60 per cent. is a rarity, and the number of corpuscles is not commonly below three millions per cubic millimetre. The reductions run approximately parallel, and the colour index is therefore usually in the region of unity. Cases in which severe anæmia is present are not unknown, but this state of affairs is not usually a permanent one; it represents an acute exacerbation of the chronic malady, and is usually only transient. Kahn mentions a case in which the red corpuscles fell to 1,310,000 per cubic millimetre, and the hæmoglobin to 20 per cent. Recovery from such an acute hæmolytic crisis usually takes little more than one month (Götzky and Isaac).

Cases in which anæmia is extremely slight, or even absent, are also known. Elliot and Kanavel describe one in which the red corpuscles were 5,180,000 per cubic millimetre, and the hæmoglobin 100 per cent.

Cases with a colour index above unity have frequently been recorded, but it is very doubtful whether such a condition really occurs in the hereditary cases.

The most constant abnormality found in stained films of blood from these cases is anisocytosis of slight degree ; some increase of this condition occurs during acute crises with progressive anæmia, but it never becomes really well marked. The anisocytosis shows itself mainly as microcytosis, and corpuscles larger than normal are quite rare.

There is no adequate evidence that poikilocytosis ever occurs.

Polychromasia is not so constant as is anisocytosis, and tends to be most marked at the periods of severest anæmia, but even then is not intense. It is well known that staining with simple solutions of methylene blue shows slight degrees of polychromasia more distinctly than does any other method, and if this stain is used it is always possible to find some polychromasic red corpuscles, even at times when other stains do not reveal them.

Nucleated red cells (normoblasts) can usually be found, but the number seen will, of course, depend upon the time spent in hunting for them : it is rare to find more than 1 or 2 per cent. of erythroblasts. Nuclear remnants, such as Jolly bodies, are found just about as infrequently as are normoblasts, and, in some cases, are absent for considerable periods. Cabot rings are absent in some cases, but it is usual to be able to find a small number. They, like the Jolly bodies, are usually found in slightly polychromasic corpuscles. Punctate basophilia is rare : I have never observed it, but Meulengracht records its occurrence in two indubitable cases.

These appearances must be regarded as evidence of intensified hæmatopoietic activity, possibly of slightly atypical character.

In normal blood, and even more in anæmias, it is possible to find a number of red corpuscles in which, with so-called vital staining, certain basophilic structures (absent from the great majority of normal corpuscles) can be demonstrated. Such elements are invariably present in considerable numbers

in the blood of sufferers from familial hæmolytic icterus, as was first emphasised by Chauffard and Fiessinger. (Reference to these vitally stainable corpuscles will be found in Appendix I.).

In normal blood, such elements rarely exceed 1 per cent. of the red corpuscles, but in all anæmias they are quite definitely increased in number : they are always at their maximum, in such circumstances, during periods of active regeneration of blood. In acholuric familial icterus the numbers are very variable at different times, and, even in the same case, may fall as low as 2 per cent. and rise as high as 30 per cent. It can definitely be stated that, during periods of marked anæmia in these patients, the number of reticulated corpuscles is high, but there is, nevertheless, no strict relationship between the number of these elements and the degree of anæmia, as is shown in some cases with large numbers of these corpuscles and practically no anæmia at all. It seems to me, however, that there is a close relationship between the amount of hæmolysis and the number of vitally stainable corpuscles ; periods of intenser jaundice are accompanied by increase of these elements, although the anæmia does not necessarily increase. There can thus be but little doubt that these corpuscles are to be regarded as evidence of active regeneration. The more intense jaundice must be due to a greater activity of blood destruction, and, if anæmia does not accompany it, there must be a very great degree of regeneratory activity ; such a condition of affairs will be accompanied by the presence of very numerous reticulated red corpuscles in the circulation, *i.e.*, it could well be regarded as a state of almost completely compensated anæmia. Further, it can justly be presumed that any case of jaundice in which reticulated red corpuscles are not increased in number is not due to hæmolysis.

The persistent microcytosis, which was first pointed out by Chauffard, is of great interest ; he also showed that this decrease of average diameter distinguished acholuric familial

icterus from all other forms of jaundice because these latter are always associated with an increased diameter of the red corpuscles. Naegeli has shown that this decrease of diameter is not accompanied by decrease of the average volume of the corpuscles; this is due to the fact that these microcytes are much more spherical in shape than are normal corpuscles.

Nothing is really known of the cause of the formation of these abnormal elements; they have variously been regarded as being the result of a primary malformation of the erythropoietic system, as representing a special form of regeneration, or as resulting from the long-continued action on the marrow of substances liberated by the persistent destruction of red corpuscles.

The increased fragility of the corpuscles in the presence of hypotonic saline was first pointed out by Chauffard, and is now recognised as a very typical feature of the disease.

It is well known that distilled water causes the destruction of red corpuscles almost instantaneously, while physiological saline solution will preserve them for a considerable time; in the former case the solution becomes a transparent red (laking of corpuscles), while in the latter the mixture remains turbid. If a series of saline solutions of different strengths be prepared, and red corpuscles be exposed to the action of each one, it is found that, in one of the solutions, some, but not all of them, will become laked (lysed), but ultimately a very dilute solution will be found in which complete lysis will take place. Normally it is found that a solution of 0·44 per cent. salt in water occasions a very small amount of hæmolysis—just enough to be recognised—but a solution of 0·34 per cent. results in lysis as complete as that caused by distilled water. Salines of strengths intermediate between 0·44 per cent. and 0·34 per cent. cause a progressively greater hæmolysis, but the process is not complete in any one of them. A variation of 0·02 per cent. in either direction is not beyond normal limits, but is not very

common, *i.e.*, the resistance curve is a very stable one. Such facts make it obvious that not all corpuscles have the same degree of resistance to hypotonic saline; the least resistant undergo lysis at 0·44 per cent., while the least fragile are just not lysed at 0·36 per cent.

These investigations can thus not give us more than information as to the greatest variation of fragility, but it is clear that any collection of red corpuscles is composed of a variety of individuals. The terms maximum and minimum resistance explain themselves, and "middle resistance" is often applied to the state in which about half of the corpuscles undergo lysis.

In all cases of acholuric familial icterus there is a general decrease of resistance of the red corpuscles; in other words, the concentration of saline at which hæmolysis begins is greater than normal. Meulengracht has seen a minimal resistance at 0·86 per cent. Sometimes the increased fragility is less striking; it may rise as high as 0·56 per cent. only, but this is rare. Complete hæmolysis occurs at a stage when the majority of normal corpuscles would not have dissolved; there is, in a sense, a shift to the left of the resistance, *i.e.*, a general weakening of the corpuscles; this is associated also with an increased range of strengths capable of causing lysis.

There are no very striking changes in the *leucocytic blood picture:* leucocytosis or leucopenia may occur, but usually the number of white cells is about normal. It is not uncommon to find a few myelocytes, and a slight degree of monocytosis is quite common. In association with crises, there is often a neutrophilic leucocytosis, and myelocytes are more numerous.

Only a brief reference to the *icterus* of the disease can be made here, but it is obviously a very important feature. In the mildest form the jaundice manifests itself only by an increase of bilirubin in the blood, and of urobilin in the urine. It is much more usual, however, for some discolouration of the skin and scleræ to be noticeable.

The fæces are highly coloured and contain great excess of urobilin and urobilinogen ; it is obvious from this that the amount of blood destruction must be very high.

It can justly be supposed that the jaundice results from the production of a quantity of metabolic products too large to be dealt with adequately by the cells, which normally deal with the formation and excretion of bile.

Splenomegaly is an invariable feature of the disease, but in rare cases may not be clinically appreciable. Usually there is increase in size of the spleen during periods of more intense hæmolysis, but in many cases the size of the organ does not vary at all during the whole course of the disease.

Our knowledge of the *anatomical changes* in acholuric familial icterus is not very profound because reliable reports in the literature are scanty ; more information has been obtained from the examination of spleens removed by operation than from autopsy.

Increase in size of the spleen up to about ten times its normal weight may occur. Most usually the capsule is tightly stretched, but is not thickened or adherent to other organs ; slight thickening and a few adhesions are, however, not unknown. The organ is extremely vascular, and is slightly softer than normal.

Microscopically, the most striking feature is the great vascularity of the pulp. It is usual to find some degree of hyaline change in the arterioles, particularly in their media. Guizetti describes a similar alteration in the walls of some of the veins of the pulp. Meulengracht has not been able to confirm either of these changes in five of his cases, but there can be little doubt that they are fairly common. The Malpighian bodies are always rather scanty, and usually show signs of slight atrophy or even of fibrosis. Guizetti regards the fibrosis of the follicles as occurring in a manner similar to that seen in Banti's disease, viz., as a sort of fibro-adenia spreading outwards from the degenerated central arteriole.

The changes in the pulp seem to be the really important

ones, and are of quantitative rather than qualitative character. The whole of the pulp parenchyma is very vascular, but the sinuses are usually practically empty. In the normal spleen, there seem to be about as many red corpuscles as nucleated cells in the pulp, but in this disease the corpuscles are far in excess of any other type of cell. The endothelium lining the sinuses, which are practically empty and collapsed, is distinctly altered. The lining cells are increased in size to such an extent as to resemble epithelial cells from a glandular organ. No changes in the reticulum have been detected. It is striking that myeloid metaplasia has never been seen in this disease. Meulengracht states that typical erythrophages are also not seen. The amount of pigmentation is variable, but in no case is it at all plentiful.

The bone marrow has very rarely been examined, but Guizetti states that in his case it was enormously hyperactive, and practically all the fat had disappeared. Microscopically there was enormous erythropoietic activity, and a relative scarcity of leucocytes. Iron-containing pigment was scanty, whereas in Eppinger's case it is said to have been plentiful.

The liver shows little change, but granules of yellow pigment, both ferruginous and non-ferruginous, are quite common. Slight fatty degeneration of the cells in the outer parts of the lobules is rarely absent. Erythrophagocytosis on the part of the Kuppfer cells may be well marked, and it is usual to find a small number of clots composed of bile in some of the smaller channels. No signs of cholangitis have been seen in any case.

The other organs show very little of interest. As has already been mentioned, Minkowski found much ferruginous pigment in the renal cortex, and Tileston and Griffin found a similar pigment in the cells of the convoluted tubules, but no other writers mention abnormalities of the kidneys.

Guizetti describes hyperplasia of the carotid bodies in one case ; the appearances led him to regard the carotid body as

functioning as a hæmo-lymph gland, but all the ordinary lymphatic glands appeared to be quite normal.

Uratic deposits about various joints are quite commonly found at autopsy ; and are also usual clinical findings.

The *complications* of the disease require brief mention. The presence of gall stones is almost invariable in all those patients who live sufficiently long. Presumably they arise by precipitation from the bile, which is, of course, excessively rich in pigment.

Increased formation of uric acid is invariable, and may, as has been mentioned, result in the formation of gouty deposits ; the excretion of this substance in the urine is also above normal. Febrile attacks of unknown origin very commonly occur, and tend to disappear as incomprehensibly as they came.

The most interesting feature of the disease is the hereditary incidence, and it is to Meulengracht that we owe most of our accurate information on this subject. Here we cannot say more than that the disease behaves as a " dominant " in the Mendelian sense. As a result, half the children of a sufferer from the disease will also have the malady while the other half will not. This does not take into account the chance of the malady arising in an individual as a true mutation : a possibility which must always be borne in mind.

The disease is typically a congenital one, but is not always noticed in early infancy, although in all cases there is a history of severe icterus neonatorum. In many cases, however, the disease has been detected in the first year of life ; it is, nevertheless, surprising how frequently the malady is overlooked for years, and is discovered quite accidentally as the result of exacerbation of one of the characteristic symptoms. Quite frequently the disease is detected in the relatives of a patient only when they are examined in the attempt to confirm the familial incidence of any given case.

It is particularly in the mild cases that diagnosis may be long delayed on account of the mildness of the symptoms

(" formes frustres " of Armand-Delille and Feuille). Even in severe cases, however, there is little tendency for the disease to shorten life, and death is almost always the result of some intercurrent malady. The patients may look very ill, but, as a rule, Chauffard's statement that they are " plus des ictères que des malades " is perfectly true.

Even in the mild cases there may be periods of intensification of the pathological process, associated with increased jaundice and anæmia. Acute reduction in the number of red corpuscles and of hæmoglobin (hæmolytic crisis) is less common and occurs mainly in cases which are primarily severe. The onset of such crises is often preceded by psychic disturbances, such as rage. The relationship to the attack is not understood. Quite mild infections will often result in a crisis, as will also severe bodily exertion.

There is really only one method of treatment which is of any importance, viz., splenectomy ; this operation is followed by complete recovery in a clinical sense. The use of X-rays over the spleen has not given much good result, although Parisot and Huelly record great improvement in two cases treated in this way.

Splenectomy is followed by an immediate rise in the percentage of hæmoglobin and in the number of red corpuscles, which both reach normal values in a very short time. The question whether the cure is a permanent one cannot be answered with certainty, but Dawson has described a patient who was in good health twenty-seven years after the operation.

Within the first few days after splenectomy the polychromasic corpuscles disappear from the circulation, and reticulated ones are reduced to normal numbers or even lower figures. The microcytosis diminishes, and the average size of the red corpuscles is increased, but there is no record of a return to normal average size of corpuscle.

There is also definite increase in the resistance of the corpuscles to hypotonic saline solutions, but again the normal

condition is not attained. Even in Dawson's case the fragility was slightly excessive twenty-seven years after splenectomy.

Jolly bodies are common in the corpuscles after splenectomy, but this is, of course, not peculiar to acholuric jaundice: in fact, it is seen in all cases after removal of the spleen.

Leucocytosis, which is invariable after splenectomy performed for other reasons, also occurs in this disease after operation. The increase of leucocytes persists for many months, and is always mainly a neutrophilia, but there is also an increase of eosinophiles. The only immature cells found are metamyelocytes in considerable numbers and myelocytes in small quantity.

Operation is followed by disappearance of the icteric tinge of the skin in a few days and by disappearance of the bilirubinæmia in about a week.

It is obvious, of course, that operation is not essential in all cases; those persons who suffer but little disability from the disease may prefer to retain their spleens, and as the disease does not imperil life there is no good reason for insisting on operation.

The greatest difficulties arise in a discussion of the *pathogenesis* of this extraordinary malady, of which the pathological features are so easily appreciated, but of whose essential nature we know so very little.

It is obvious that the jaundice is purely a secondary phenomenon, and we are therefore left to decide whether the changes in the spleen or the alterations in the character of the red corpuscles are the essential feature of the malady.

There can, of course, be no doubt that excessive hæmolysis is characteristic of acholuric familial jaundice, because, even when anæmia is absent or very slight, there is persistent bilirubinæmia. Further, there can be no argument about the site of this hæmolysis: it is certainly mainly in the spleen, and therefore disappears after splenectomy.

The questions that arise are thus :—

Is there excessive hæmolytic action of the spleen on otherwise normal corpuscles ? or

Are abnormal corpuscles presented to the spleen, which destroys them, as being elements foreign to the circulation ?

It seems that there are more writers in favour of the second view, but supporters of the first conception are quite numerous. It is very important to repeat Grawitz's warning that there is no good evidence that all red corpuscles, which are unduly fragile *in vitro*, are equally non-resistant *in vivo ;* but many theories of the pathogenesis of acholuric familial icterus have ignored this just remark.

It is generally admitted that the spleen is capable of destroying effete red blood corpuscles, but less attention has been paid to what Botazzi calls the " hæmocatatonistic action " of the organ. He states that corpuscles in the splenic vein are less resistant to the action of hypotonic saline than are those in the artery. He concludes that the spleen must have some injurious action even on those corpuscles, which it is unable to destroy. The conception of a primary hypersplenism as the essential fact of the disease is thus a little more complicated than it would seem to be at first sight.

The hyperactivity of the bone marrow in this disease can well be regarded as a secondary phenomenon resulting from the stimulation by the products of excessive destruction of corpuscles. McMaster and Haessler showed that hyperplasia of myeloid tissue could occur only if a sufficient amount of iron were available; in this way they explain the much greater speed of regeneration of anæmias due to hæmolysis, as compared with post-hæmorrhagic ones. It seems only rational to presume that myeloid hyperplasia would result from any condition which caused excessive blood destruction in the body.

The excessive fragility of the red corpuscles and the micro-

cytosis must now be regarded as being purely secondary phenomena, but whether due to an atypical form of regeneration in the marrow or whether entirely as a result of the excessive hæmacatatonistic action of the spleen cannot be definitely determined. The incomplete disappearance of these phenomena after splenectomy suggests that the marrow has " got into a habit " of producing unusual corpuscles ; if the hæmocatatonistic action of the spleen were the sole cause, one would expect removal of the organ to be followed by complete disappearance of these abnormalities of the corpuscles.

The heredo-familial incidence of acholuric icterus is quite certain, but it cannot be claimed that we have evidence that there is no additional external factor in its development. It is conceivable that the familial incidence depends more upon an inherited susceptibility than upon a direct handing on of the disease-process ; it must be admitted that no such external factors have ever been detected, but it is well to bear in mind their possible importance.

It is certain that, in addition to the cases in which a family history can be obtained, there are others in which the patient seems to be the sufferer from a disease-process peculiar to himself. The clinical picture in these cases is identical with that of the familial ones, and splenectomy has an equally good effect on the disease. It seems almost certain that these persons must represent the first generation in which the underlying mutation has appeared, but, unfortunately, we are not as yet acquainted with the history of their offspring.

There is another group of cases which is usually included under the term *acquired hæmolytic icterus*, and it has been unfortunate that many writers have seen fit to regard this disease as being related to the heredo-familial one. Pictures identical with these of the " acquired " disease can be produced by the action of a variety of hæmolytic poisons, *e.g.*, phenylhydrazin hydrochloride, toluylene diamine. There can be little doubt that a variety of different diseases has been

included under the name " acquired hæmolytic icterus," and it is not yet possible to assign all of them to their proper categories.

Certain known ætiological agents, such as malaria and syphilis, may cause hæmolytic icterus, as may also pregnancy ; there are, nevertheless, some cases in which the cause cannot be discovered (cryptogenetic acquired hæmolytic icterus of Brulé). Such cases occur most commonly in middle-aged women ; they run a long benign course and may fairly closely resemble the familial disease. The French state that a most striking phenomenon in these cases is the occurrence of auto-agglutination of the red corpuscles, *i.e.*, agglutination of the patient's own corpuscles by his own serum. This is only known as the result of *in vitro* experiments, and whether it occurs *in vivo* is not known.

It is tempting to imagine that some at least of these cases may represent late development of typical symptoms in a person bearing the mutation characteristic of familial hæmolytic jaundice, but such a view is negatived by the fact that the patients with the acquired disease do not transmit their disability. It is very striking that, although there is greatly increased fragility of the red corpuscles, there is no microcytosis in the acquired malady ; in fact, Meulengracht states that macrocytosis is quite commonly seen.

Great though the gaps in our knowledge of this disease may be, we are justified in regarding it as being essentially different from the familial form.

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CHAPTER XIV

SPLENOMEGALY

IV. Anæmia pseudo-leukæmica Infantum

This disease is difficult to describe for a variety of reasons : mainly because it does not seem to represent a very well-defined entity, and also because we do not understand at all completely the details of the mode by which the immature human organism reacts to various stimuli. It is obvious that the hæmatological accompaniments of various diseases, which occur both in children and in adults, will differ according to the normal blood-picture of the individual and according to its power of reacting to the noxious stimulus. The blood-pictures of infants and adults are very different, and it seems quite reasonable to suppose that their reactivity is also very different.

Most anæmias occurring during the first three or four years of life are accompanied by swelling of the spleen, although there can be but little doubt that the conditions are not all of the same ætiology.

Von Jaksch, as is well known, was the first to call attention to a disease occurring in infants, and characterised by splenomegaly, enlargement of lymphatic glands, anæmia, and extreme leucocytosis. Von Jaksch himself realised that the distinction of the disease from the true leucoses was a difficult one, and all the signs, which he regarded as being of differential significance, are often common to both diseases, *e.g.*, the small number of eosinophiles and basophiles in the infantile malady, but a similar state of affairs may be found in leucosis.

It is doubtful whether the typical disease occurs after the

age of three years ; the symptoms usually appear during the second three months of life, but may not manifest themselves until later. There seems to be no doubt that the malady is rare in breast-fed children, and its appearance is favoured by unsuitable diet. The occurrence of identical symptoms in twins has frequently been noticed. The majority of the cases are seen in children suffering from severe rickets, but syphilis and even gastro-intestinal derangements seem to be of ætiological importance.

The anæmia may be very severe (as low as 500,000 red corpuscles per cubic millimetre), and, indeed, is always very well marked. The colour index is practically always below unity, but slight rises have been recorded.

The degree of leucocytosis is always very considerable ; usually there are between 30,000 and 40,000 leucocytes per cubic millimetre, but in von Jaksch's original case there were 114,000 per cubic millimetre.

Anisocytosis and poikilocytosis are always present, as are also polychromasia and punctate basophilia.

Nucleated red cells are always present in very considerable numbers, and it is striking to notice that karyokinesis is common in the larger cells.

Platelets are practically always diminished.

In very young children suffering from the disease it is usual to find that the leucocytosis depends upon the presence of a great excess of lymphocytes. Ordinary neutrophiles are present in decreased percentage numbers, and myelocytes are practically never absent from the blood-picture.

Rarely cases are seen with no leucocytosis, but the qualitative changes in the blood-picture are the same as in those with increase of leucocytes.

In fatal cases, which are not common, the number of leucocytes usually rises steadily and is associated with a progressive increase in the number of immature myeloid cells.

There also seem to be cases in which the clinical signs are the same as those already described, but the hæmatological

picture differs inasmuch as there is neutrophilic leucocytosis ; almost all writers are agreed that this is a much less common condition of affairs.

The histological changes in the organs seem to differ in very many particulars from those of the leucoses. In cases in which lymphocytosis has been well marked there is lymphatic hyperplasia, but there is never formation of peri-portal lymphomata, as in lymphadenosis. Myeloid metaplasia in the liver is always well marked, and a similar condition is common even in lymphatic glands. Non-granular cells are very numerous in the bone marrow, but I have been unable to decide whether these are myeloblasts, as stated by Naegeli, or erythrogonia, as contended by Helly.

The ætiology of the disease is far from being understood, but it is commonly accepted that rickets is an important factor ; this is, however, denied by Kleinschmidt, who attributes all the pathological changes to alimentary disturbance (see below).

In any case, there can be no doubt that the peculiar characters of the disease result from the special reactive powers of the infantile organism ; in fact, Reckzeh has been able to produce the disease in young animals by injections of hæmolytic poisons, although such a reaction is never obtained in the adult.

Therapeutic measures are practically limited to the treatment of any associated malady, *e.g.*, rickets, syphilis, etc., but in all cases arsenic seems to be of considerable value. In some cases which have not responded to medicinal treatment splenectomy has been performed with excellent results (Johanson).

Reference has been made above to Kleinschmidt's contention that alimentary disturbance may be the cause of von Jaksch's anæmia ; he even goes so far as to attribute the majority of the common anæmias of childhood to unsuitable dietary. Although many writers are not prepared to agree completely with Kleinschmidt's views, it is very necessary to give a summary of his contentions.

It has been amply demonstrated that simple starvation does not result in any notable alterations in the composition of the blood-picture ; and it seems justifiable to presume that long-continued malnutrition, short of complete starvation, is equally unable to cause anæmia. The question as to the effects of a diet, which is defective in the sense of improper balance of its constituents, requires a longer answer. There can, of course, be no doubt that infantile anæmias are commoner among the children of the very poor than among any other class of the community, and it is obvious that these are individuals whose ration of protein is likely to be much restricted.

The experiments of von Hösslin throw some light on the subject. He found that dogs kept on a diet very defective in iron did not become anæmic, but did not return to a normal blood-picture after a severe hæmorrhage. It is very striking that he was able to induce such changes only in puppies, *i.e.*, in rapidly growing animals. Anæmia is particularly likely to occur if infants, who have just been weaned, are placed on a diet deficient in iron, or even if they are fed purely on milk for too long a time. This fact is explained by the observation of Bunge, who showed that at the end of the suckling period the amount of iron in the infantile organs was at a minimum, whereas it had previously been able to carry on with the relatively extensive iron depôts at its command, *i.e.*, during the normal period of suckling, hæmoglobin seems to be derived from iron already available in the infant, but, after that period, more iron must be supplied in the diet if adequate formation of hæmoglobin is to take place. Further, it can be shown that addition of iron to a diet already containing a sufficient quantity has no effect upon the blood, whereas its addition to milk will make that substance a good and sufficient diet.

It is very interesting to realise that a diet poor in iron does not cause anæmia in pregnant mice : and their offspring, although possessing less iron than normal in their tissues,

are not anæmic. If this new generation be kept on a diet poor in iron during pregnancy the third generation of mice will show very severe anæmia, which can be improved and even cured by administration of iron in early life.

Numerous French writers have called attention to anæmia occurring in infants between the ages of twelve and thirty months in which neither rickets nor intestinal disturbance seem to play any ætiological rôle. These children were often found to have been either premature or twins. Too greatly prolonged feeding with milk seems to account for the anæmia, and cure is rapidly brought about by the administration of ordinary mixed diet. The anæmia has one very distinctive feature in that it is practically a pure oligochromæmia, *i.e.*, there is well marked reduction of hæmoglobin and a practically normal number of corpuscles.

Czerny devoted a considerable amount of attention to the subject of *alimentary anæmia*, and reached the conclusion that simple defect of iron was not sufficient to account for the occurrence of the anæmia ; he contended that some constitutional anomaly must also be present. He based his view, in part, on the fact that simple addition of iron to the diet of these children did not result in disappearance of the anæmia : a mixed diet was absolutely essential for cure. Further, he showed that some cases of infantile anæmia associated with enlargement of the spleen would also recover after being supplied with a varied full diet. He, therefore, concludes that the picture of anæmia pseudo-leukæmica infantum may occasionally depend entirely upon " alimentary anæmia," although he admits that the majority are of infective or rachitic origin.

A more detailed account of alimentary anæmia may here be convenient, because, although Kleinschmidt published his results in 1916, the characters of the malady are less well recognised than should be the case.

The majority of the children are between three months and two-and-a-half years old, but cases in infants under three

months and in children up to five-and-a-half years are recorded.

In forty-five cases, Kleinschmidt found twelve premature infants, nine twins, three triplets, and five infants, who were stated to have been very weakly at birth. He also states that other peculiarities were quite common, *e.g.*, spasmus nutans, pylorospasm, laryngospasm, and mental deficiency. Very noticeable was the hyperæsthesia of the sense of taste in all his cases.

As Czerny pointed out, there is almost always hyperplasia of lymphatic tissue ; not only is the spleen enlarged in many cases, but the tonsils are also hyperplastic. It is strange to find that some cases show splenomegaly and no tonsillar enlargement while others show the opposite condition.

It is rare, but not unknown, for a case to show no clinical evidence of excess of lymphatic tissue. It is very important to realise that the splenomegaly is almost always present before anæmia has developed ; and there is no obvious relationship between the size of the spleen, which may be very great, and the degree of the anæmia.

Rickets is extremely common, and, as is well known, this is often accompanied by enlargement of the spleen, but we are quite ignorant of the relationships of these three phenomena, viz., anæmia, splenomegaly and rickets.

It is obvious that our knowledge of infantile anæmias, due to defective feeding, is in its infancy, but the very fact that they do exist should always be borne in mind in any attempt at the classification of the anæmias of the first years of life.

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SUMMARY

It must be made clear at the beginning of this chapter that it is hoped to do more than present a simple summary of the contents of the rest of the book ; an attempt at correlating all known hæmatological phenomena is to be made, but with a lively sense of the woeful deficiences of the writer's knowledge. In places there are great gaps, due to a failure to appreciate the relations of one set of phenomena to another, although probably they are obvious ; in other places it may be objected that totally dissimilar phenomena have been grouped together, and the writer can do no more than apologise for such a forcing of the facts, which may, however, form a temporary working hypothesis.

There is probably no set of tissues the comprehension of which is so much facilitated by a study of embryology as the hæmatopoietic organs, but, unfortunately, there are still fundamental discrepancies in the views of different writers. In a sense it may be said that the whole life-history of the blood-forming tissues is an embryonic one, because at no time do they represent even an approximately completed set of organs. The fact that the details of the ante-natal development of hæmatopoietic tissues form the subject of so much debate prevents us from being certain of the importance of congenital malformations of the system in the production of pathological conditions. This difficulty is further enhanced by the fact that hæmatopoietic tissue, at least its lymphatic component, is so very widely distributed that considerable quantitative variations might occur and remain unnoticed.

The evidence that constitutional anomalies of hæmatopoietic tissue occur is only indirect, *e.g.*, the observation of various diseases occurring in several members of the same

family. When we recollect that familial incidence of " diseases of the blood " is comparatively common, we are led to presume that congenital abnormalities of the hæmatopoietic tissues must be relatively common.

A constitutional peculiarity might be an obviously morphological one, such as the persistence of megaloblastic tissue in the livers of persons in whom pernicious anæmia might occur, or they might be of a more subtle character and manifest themselves mainly by some peculiarity of reaction to stimuli, which, in ordinary people, led to a different result. Further, it is conceivable that abnormalities of hæmatopoietic tissue can be acquired in post-natal life ; a fairly obvious example occurs in typhoid fever, where hyperplasia of lymphatic tissue, *e.g.*, in the portal tracts of the liver, is usual. Such hyperplastic lymphomata could well be regarded as possible morphological abnormalities upon which the typical appearances of lymphadenosis may become superimposed.

Again, we have to remember that a congenital peculiarity is not, of necessity, a permanent abnormality ; it is conceivable that it may gradually disappear as in the case of megaloblastic anæmias in infants, who are not, therefore, inevitably burdened with a persistent remnant of megaloblastic tissue for the rest of their lives.

Enough has been said at this point to indicate that, in our conception of diseases of hæmatopoietic tissue, we must never neglect the consideration of the nature of the soil on which the malady is implanted.

It is probably very rare for a congenital anomaly of the hæmatopoietic tissues to be so extreme as to result in manifest disease without the interposition of some further stimulus. Such environmental changes could be either internal or external.

Metabolic changes can result in well-marked alterations in the blood-forming tissues, but there is rarely much concomitant variation in the blood. The striking histological pictures

of Gaucher's disease and of diabetic lipoidæmia show how a metabolic peculiarity can influence the reticulo-endothelium.

External stimuli are, of course, most usually bacterial in nature ; and we find that they are, almost invariably, accompanied by changes both in the blood and the hæmatopoietic tissues. The alterations are, in a sense, all reactive, but some are manifested by a positive and others by a negative response. Negative response may result either from the action of a toxin directly inhibiting cytopoiesis or from an unusually large dose of one, which, in smaller concentration, causes positive reaction.

Although not invariable, there seems to be a definite tendency for coccal infections to be associated with neutrophilia (absolute or relative), with definite shift to the left, whereas many bacillary infections are accompanied by lymphocytosis (relative or absolute), together with a shift to the left of the neutrophiles.

Although the lymphatic and myeloid tissues seem, in so many ways, to be very distinctive, there are certain obvious inter-relationships. This fact is demonstrated by the occurrence of increase of lymphocytes after infections accompanied by neutrophilia, although the lymphocytes had been much reduced during the height of the infective process.

Unfortunately there is a very large group of diseases in which no comprehension of the nature of the pathological process can be obtained, and their classification must be left to the future.

It is very difficult to escape the belief that every pathological change, and, indeed, every physiological variation, must be accompanied by hæmatological changes, which we are prevented from observing only by the defects of our technical methods.

APPENDIX I

Some Notes on Hæmatological Technique

It is not the present intention to describe all the well-known methods of examination of the blood, but a few remarks on the more recent improvements may not be out of place.

There is but little to mention in relation to the methods of **Enumerating Red Corpuscles and Leucocytes**, but there can be little doubt that the use of an automatic diluting pipette is a great advantage (Pincy, 1). The diluting fluids in ordinary use are quite satisfactory for the red corpuscles, but a solution of acetic acid stronger than that commonly advocated is essential for the leucocytes. If a strength less than 3 per cent. of acetic acid be used, it is very common to find remnants of red corpuscles in the counting chamber; even 5 per cent. solutions can well be employed.

It is now customary to use hæmocytometers of the "Bürker" type in which the diluted blood is run under the cover slip by capillary attraction instead of being placed on the counting chamber and then covered with a cover glass. This modern method has introduced one or two new difficulties. Careful **Cleaning of the Cover Slip and Hæmocytometer** have always been important, but one needs to be even more scrupulous in dealing with the modern instrument. If the surface of the counting chamber and the under surface of the cover glass are not absolutely free from grease and dust, it will be found that the diluted blood runs under the cover slip irregularly in such a manner that it lags in one place while running on in another. In this way irregularities in the distribution of the cells in the counting chamber must occur. The method of cleaning here advocated involves the necessity of having a hæmocytometer made of solid glass; the older cemented pattern is quite useless.

The hæmocytometer slide is dipped into pure nitric acid for several minutes, and is then held under running water of gradually increasing temperature until it is free from acid and is very hot. A few drops of absolute alcohol are run over the counting surface, and are followed by several drops of ether; the heat of the slide

causes immediate evaporation, and no drying or polishing is required. The cover slip is cleaned in an identical manner.

It is found that the ordinary cover slip supplied with hæmocytometers is not really satisfactory because the capillary attraction tends to cause it to curve towards the counting surface of the hæmocytometer; it is, therefore, essential to use a slip much thicker than that commonly used. Allport suggested a cover slip of 4 millimetres in thickness, and, although this will of course not bend, it has the disadvantage that a low power objective and a high power eye-piece have to be used on the microscope. A cover slip of 1 or 1·2 millimetres will not bend, and permits of the employment of the ordinary "sixth" objective.

The preparation of **Films for the Differential Count** should, in my opinion, always be done on cover slips. Slides offer several advantages, *e.g.*, they need not be covered with a slip after being stained, the name can be scratched on the film itself, and scrupulous cleanliness is not very essential.

The greatest objection to preparing films on slides lies in the fact that some part of the drop of blood remains on the slide or other object that is used for spreading the blood on to the slide for examination; and it is, of course, quite impossible to determine what types of cells have been left behind, but it is very probable that different cells have a different degree of adhesiveness to glass, and, if this is so, an accurate estimate of the blood picture will be impossible. If cover slips are used, one obtains two films from each drop of blood. Both of these films should be stained and examined. For example, if one has determined to count 500 leucocytes, 250 should be counted on each film; in this way a very fair estimate of the cellular composition of a whole drop of blood will be obtained.

Again, coverslip films offer the advantage that, without using large amounts of staining solution, they can be stained face downwards in watch glasses, and so be far less liable to become covered with precipitates.

The only difficulty of this method lies in the *cleaning of the cover slips*, but a routine method can easily be found to serve all purposes. The cover glasses should be placed in pure nitric acid for twelve hours or longer, washed in running water for the same length of time, swilled with distilled water, and kept in absolute alcohol until required. Just before use, the requisite number of slips should be removed from the alcohol with forceps and dried and polished before making the films. It is best to handle the slips with cover slip forceps, but after a little practice

it is possible to hold them by their edges and so avoid soiling the surface ; if this can be done forceps are unnecessary.

In *making the film* a little experience is required before the correct size of the drop of blood can be judged. The drop is taken in the middle of one slip, and after a moment's pause to permit of the steam around the drop disappearing a second cover slip is lowered on to it in such a manner as to leave the corners projecting. As soon as the blood has spread to the edges of the slips by capillary attraction they are separated with a quick lateral movement, and are placed face upwards to dry prior to staining.

There are, as is well known, a great variety of hæmatological stains, but here only one will be described, and, although it is a little more troublesome than the others, it has so many advantages that the slightly greater length of time required is very well spent.

The method is essentially that published by Pappenheim under the name of "*panoptic method.*"

Air-dried films can be stained immediately, but it is my experience that the best results are obtained if the films are kept for about twenty-four hours after preparation before staining them.

The cover slip is placed in a watch glass with the blood downwards ; a suitable amount of stain (1 c.c. with an ordinary watch glass) is gently run under the film, and the watch glass is covered to prevent evaporation. The stain to be used is May-Grünwald's solution, but if this is not available Jenner's stain is almost as satisfactory. The undiluted stain is allowed to act for three minutes, and then an equal amount of neutral distilled water is added and the mixture allowed to act for a further one minute. (Even better results are obtained if the stain is diluted with the solution suggested by Russell Haden, viz., 6·63 gm. of chemically pure re-crystallised acid potassium phosphate and 2·56 gm. of anhydrous basic sodic phosphate in 1 litre of distilled water ; this solution should have a *p*H of 6·4.) For ordinary purposes simple distilled water is sufficient. The film is removed from the diluted May-Grünwald or Jenner solution, and is transferred without washing into a diluted solution of Giemsa's stain or of "Panchrom" (which is a modified Giemsa stain, and is preferable to the original preparation). The diluted Giemsa or Panchrom consists of one drop of the stain to each 1 c.c. of distilled water (or preferably Haden's solution). The film remains in the diluted Giemsa or Panchrom for six to ten minutes. It is then removed and washed for thirty seconds with distilled water or Haden's solution, and is waved about in order to dry it *at room temperature.*

This method gives very excellent results, but there is always a rather dirty appearance of the granules, which can be overcome by a special addition to the diluted Giemsa solution. Ehrlich long ago described the so-called "*triacid stain*," which gave very beautiful staining of granules, but rendered very little nuclear detail. The staining of the granules depended upon the presence of methyl green and orange G in the staining solution. If watery solutions of methyl green and orange G be mixed a heavy precipitate is obtained ; this can be dried and dissolved to saturation in pure methyl alcohol. One or at most 2 drops of this solution, which keeps indefinitely, should be added to the diluted Giemsa or Panchrom solution used in the method given above.

A summary of the definitive method can now be given :—

1. Stain the air-dried film (preferably after leaving for twenty-four hours at room temperature) in May-Grünwald's stain (Jenner's solution will do, but is not so good) face downwards in a covered vessel for three minutes.

2. Add an equal amount of neutral distilled water (or preferably Haden's solution) and stain for one minute more.

3. Place the film (without washing) into the following solution : Neutral distilled water (or preferably Haden's solution), 5 c.c. ; Giemsa's stain (or preferably Panchrom), 5 drops ; orange G-methyl green compound saturated in methyl-alcohol, 2 drops. Stain in this mixture for six to ten minutes.

4. Wash with distilled water (or better with Haden's solution) for thirty seconds.

5. Dry as rapidly as possible at room temperature. Heating to expedite drying results in disappearance (partial or complete) of azurophilic granules. Blotting is liable to leave bits on the film, and should therefore be avoided.

6. Mount the film in Canada Balsam on a thin slide. If very fine detail is required it is better to mount the film in euparal, which has a lower refractive index than balsam. Even better results can be obtained in the examination of very immature cells, *e.g.*, myeloblasts or lymphoblasts, by mounting in green euparal, the colour of which intensifies the blue staining of the cells. In any case, for the sake of the permanence of the preparations, a neutral mounting medium should be chosen.

In the **Examination of Films** there can be no doubt that an apochromatic objective is a great advantage ; this is not so much on account of its apochromatic character as on account of the generally better workmanship of these instruments. It is, however, not much use employing an apochromatic objective unless

the condenser is of equal quality, and, in any case, an oil immersion condenser should always be used. Further, it is essential that the optical arrangements should be very carefully adjusted (Piney, 1926), and very careful centring of objective and condenser should precede each examination. The source of light should be sufficiently small to be focussed in the field of the microscope so that one can make sure of obtaining critical illumination. There is really no better method of illumination than the use of the edge of the flame of an oil lamp, which must, of course, have a chimney flattened on one side. Careful focussing will enable one to get the flame sharply focussed in the field of the microscope, and when this has been achieved the sides of the field will be dark, while there is a bright triangle in the middle. It is in the centre of the field, *i.e.*, in the middle of the bright triangle, that each cell should be examined.

This stain supplies one with preparations in which extremely fine detail can easily be observed, but the very slightest degrees of polychromasia and of punctate basophilia may escape notice. In the rare cases in which it is essential that even the most minute trace of either of these conditions should be recognised, it is well to stain a film with a simple solution of methylene blue. Preliminary fixation for about ten minutes in methyl-alcohol followed by staining for about the same length of time in Unna's alkaline methylene blue, washing and mounting in Balsam complete the preparation of the film.

Neither of these methods is capable of showing the presence of *reticulated red corpuscles*, and for this purpose **Vital Staining** is essential. Many methods have been suggested and are all fairly good. The following is quite sufficient for all ordinary work :—

A drop of a saturated solution of brilliant cresyl blue in absolute alcohol is placed on a clean and slightly warmed cover slip. The drop is spread evenly over the slip with a glass rod, and the alcohol evaporates, leaving a thin film of the dried stain deposited on the glass. A drop of blood is placed on a clean slide, and the cover slip lowered on to it. At the end of about thirty minutes staining is complete. It is often an advantage to prepare more permanent preparations, and this can be done by a slight modification of the technique described above. A drop of the alcoholic solution of brilliant cresyl blue is placed at one end of a microscopic slide and is spread out to an area of about 1·5 mm. with a glass rod. If a thick margin of stain is present after evaporation of the alcohol, it should be wiped off. Large numbers of slides can be prepared for stock as no deterioration of the dried stain occurs. A drop of

blood is taken on a clean square cover slip and dropped on to the stain. The blood spreads out evenly and the stain immediately goes into solution (such a preparation can now be examined under the microscope, but keeps for only a few hours even if the cover slip be surrounded with vaseline to prevent evaporation). A permanent preparation can be made if the cover slip is pulled off the slide by a sharp lateral tug and allowed to dry in the air. When dry, the film can be stained in the ordinary manner described above and mounted in the same way. Such a preparation keeps for several months or even for years if not exposed to light for too long a time. The reticular material stains blue, and is easily seen lying in the pink-stained red corpuscles.

Histological Examination of the hæmatopoietic tissues presents numerous difficulties. Although interesting observations can be made on sections stained by the ordinary methods, it requires special technique to demonstrate the essential hæmatological details. The staining of granules in sections of hæmatopoïetic tissues, particularly in the bone marrow, is really very difficult, and, in any case, success is possible only with material which has been fixed very shortly after death. The only method of real value is that described by *Ellermann*, which, when carefully followed, gives most admirable results :—

Small fragments of tissue (not more than 2 mm. in thickness) are fixed for twenty-four hours in Helly-Maximow solution (Zenker's fluid without acetic acid : 90 parts ; 40 per cent. formalin : 10 parts) at room temperature ; the pieces of fixed tissue are washed in running water for twenty-four hours and are passed through 70, 96, and 99 per cent. alcohol into xylol and thence into paraffin wax. Sections not more than 5 microns in thickness must be used.

The sections are treated with xylol, absolute alcohol and water in the usual manner and are then firmly blotted. They are now stained in a formol-eosin solution (neutral formalin 0·25 c.c. and 5 c.c. of a 1 per cent. aqueous solution of eosin ; the mixture must be made freshly each time) for fifteen minutes, placed in distilled water (at 45° C.) for four minutes, and then stained for thirty minutes in a mixture of equal parts of distilled water and a 0·5 per cent. methyl alcoholic solution of eosinate of methylene blue (Grübler). After placing in distilled water for five to ten minutes the sections are differentiated in 100 per cent. alcohol for two to four minutes, passed through xylol and embedded in dammar in xylol (or yellow euparal).

Absolutely freshly fixed material gives very beautiful results,

and even neutrophilic granules are clearly stained. It is often possible to get good results with material fixed twenty-four hours after death, but later than this I have never been successful. Karyokinetic figures are well shown, and this is the method of staining that Ellermann used in his investigations of the size of mitotic angles in different types of blood-cells.

Staining of reticular fibrils is necessary only for purposes of detailed investigation, and can be performed very well on tissues that have been fixed in Zenker's solution and embedded in paraffin ; this is a great advantage when compared with the ordinary Bielchowsky method of silver impregnation of frozen sections fixed in formalin.

We owe the method here described to *N. Chandler Foot*, and slight modifications based on personal observations have been introduced. I have found that, with scrupulous cleanliness, it is possible to get very consistent results at every attempt.

The tissue, as fresh as possible, is fixed in ordinary Zenker's solution, but Helly-Maximow fixative is equally good, for twenty to twenty-four hours, and is then washed in running water for twelve hours or more. It is passed through rising grades of alcohol into xylol and into paraffin wax in the usual way.

Sections, which should not be more than 6 microns thick, are fixed to the slide by egg-albumen, and, if no loss due to floating off of sections from the slides is to occur, should be dried for twenty-four hours in the oven.

The wax is removed with xylol followed by alcohol, and the section is then placed in 0·4 per cent. iodine in 80 per cent. spirit for ten minutes. The iodine is partly removed by immersion in 70 per cent. alcohol for ten minutes, and bleaching is completed by immersion in 0·25 per cent. hypo in 50 per cent. spirit (about fifteen seconds) ; this is followed by washing.

After five minutes in 0·25 per cent. aqueous potassium permanganate followed by washing, the section is placed in 5 per cent. oxalic acid in water for twenty minutes, and is then well washed and swilled with distilled water. It is now placed in 2 per cent. silver nitrate in distilled water for twenty-four hours in the dark. After swilling the section in distilled water, it is placed for thirty minutes in a solution prepared as follows :—

Twenty c.c. of a 1 per cent. solution of silver nitrate in distilled water has 20 drops of a freshly-prepared 40 per cent. aqueous solution of sodium hydroxide added to it. A brown precipitate occurs, and is redissolved with strong ammonia ; it is essential not to use an excess of ammonia, and, in order to avoid this, it is

best to add a little less ammonia than is required for complete solution of the precipitate, and filter off the last fragments. At the end of thirty minutes the section is well washed in distilled water and transferred to a 5 per cent. solution of formalin for thirty minutes. In this bath, blackening takes place, and therefore it is essential to make sure that all trace of the ammoniacal silver solution has been removed before placing the section in it. After thorough washing, the section is toned for eight minutes in a 0·5 per cent. solution of gold chloride, again washed and then fixed in 2 per cent. hypo for two minutes. The section should now be washed for several hours before using any counter stain. The counter stain may be Weigert's iron hæmatoxylin followed by van Gieson, but this has the disadvantage that the nuclei are stained the same tone as the reticular fibrils. It is rather better to use a slightly acidified solution of neutral red and so get a pink tone in the nuclei. Mounting in dammar or green euparal is better than balsam.

The method is valuable in giving an excellent idea of the distribution of the reticulum, and, if examined with high magnifications, often permits the fine intra-fibrils to be recognised.

The investigation of the **Resistance of Red Corpuscles** to the action of hypotonic saline solutions can be undertaken by a variety of methods, but the one here described, which is based on Meulengracht's technique, has been found very satisfactory.

A series of solutions of chemically pure sodium chloride is made ; the strongest solution employed is a 0·9 per cent. one and the weakest a 0·2 per cent. solution. The intermediate solutions differ from one another by 0·02 per cent.

The easiest method is to prepare a solution containing 10 gm. of chemically pure and dry sodium chloride in 100 c.c. of neutral distilled water. The different strengths can then be prepared from this 10 per cent. solution, *e.g.*, if one requires a 0·2 per cent. solution, it is necessary to take 0·2 c.c. of the 10 per cent. solution and add distilled water to make it up to 100 c.c.

The blood for examination is taken from a vein through a needle directly into a small glass vessel containing 3 drops of a 3 per cent. solution of sodium oxalate. The glass must be gently agitated during the period of bleeding, and about 5 c.c. of blood should be removed. The blood is centrifuged and the supernatant plasma is removed with a pipette ; the corpuscles are now ready for testing without washing or any other manipulation.

A series of small tubes (such as those commonly used for the Wassermann reaction) is required, and into each one are put 2 c.c.

of dilute saline. It is, of course, not always necessary to test the blood with the whole range of solutions (*e.g.*, in normal blood, only the part of the range between 0·5 and 0·3 per cent. will be needed). One drop of the thick emulsion of corpuscles is added to the saline in each tube, and the whole is then gently shaken. After several hours' standing, it will be seen that, in the most dilute salines, complete hæmolysis has occurred ; somewhere in the range partial hæmolysis will be seen, and in the strongest solutions no signs of laking will be visible. If time is important there seems to be no good reason against centrifuging each dilution instead of waiting for sedimentation to occur.

No method in which vigorous shaking to cause defibrination is used should be employed because mechanical injury to the corpuscles always occurs, and so alters the real result of the test.

The **Enumeration of the Blood Platelets** per cubic millimetre of blood presents no great difficulty, but is a laborious business. One drop of a 14 per cent. solution of magnesium sulphate is placed on the skin, which has previously been made hyperæmic, and the skin is pricked with a sharp needle. Blood wells up into the drop of magnesium sulphate solution. Films are made in the ordinary manner on cover slips from this mixture ; staining is carried out in the way already described after the films of diluted blood are completely dry. The mixture of blood with a solution of magnesium sulphate prevents the platelets from running together into agglomerations, as is always the case in ordinary films. The stained film is examined and the number of platelets relative to the number of red corpuscles is counted ; at least 2,000 red corpuscles should be counted in this method. The number of red corpuscles per cubic millimetre must be found in the usual way in the hæmocytometer, and, from these two results, it is easy to calculate the number of platelets per cubic millimetre of blood.

There are many methods available for the determination of the **Coagulation Time of Blood,** but none of them is completely satisfactory. The technique suggested by Bürker is, in many ways, the best. A small amount of blood is mixed with an equal amount of distilled water in a watch glass and is kept at a temperature of 25° C. A very finely drawn out glass rod is passed through the mixture at fifteen second intervals, and, normally, it is found that a fine thread of fibrin adheres to the rod at the end of five minutes ; this is taken to be the beginning of coagulation. The process is complete in not less than eight and not more than twelve minutes.

The determination of the **Bleeding Time** is performed according to Duke's technique. The ear is pricked with a sharp needle to a

depth of 3 mm.; the resultant drops of blood are taken off on clean filter paper at fifteen-second intervals (the wound itself must not be touched). Complete hæmostasis occurs in two or two and a half minutes in normal persons.

Fahræus has laid much stress upon the investigation of the **Suspension-Stability** of the blood. The simplest method is that of May (and it is also the cheapest apparatus). Essentially, there are ten tubes of 10 cm. length and 6 mm. diameter. The tubes stand in a special rack at the back of which is a cardboard scale with a graduation from 0 to 100. Venous blood is used, and is withdrawn with a syringe which has been well washed out with a 3·8 per cent. solution of sodium citrate, and which contains 0·4 c.c. of this solution. Two cubic centimetres of blood are drawn into the syringe; it is mixed with the citrate solution by gentle movement of the syringe. One of the tubes is held at a slight slant, and, with a fine glass cannula, 1·8 c.c. of the citrated blood is placed in it, being very careful to avoid all air bubbles. The tube is returned to the stand in a vertical position and, at the end of one hour, the level can be ascertained. The term "level" is applied to the height of the column of plasma above the sedimented red corpuscles, as read on the scale.

The normal figures appear to be between 1 and 4 in men, and between 1 and 6 in women. Figures up to 20 are regarded as slight increase, up to 40 as medium, and over 40 as great increase.

The basis of the test is the supposed alteration of the amount of plasma-globulin in various diseases, but the size and number of corpuscles also influences the result to a slight extent. An increased rate of sedimentation is found in association with a variety of pathological conditions, *e.g.*, malignant tumours; there is a physiological increase in pregnancy and during menstruation. Decreased sedimentation is often seen in association with disease of the liver.

The test should, if possible, be performed while the patient is fasting or, if this is impossible, as soon after breakfast as possible. It is obviously essential that the test should not be performed during menstruation and during the three or four days preceding and succeeding it if results of clinical value are required.

The method, which has been the subject of numerous published papers, is capable of distinguishing between non-inflammatory and mild and severe inflammatory processes, and may be of considerable use in assessing the progress of a case of tuberculosis. In the persistent absence of increased rate of sedimentation over a period of about ten days, one can state that there is no active

tubercular process in existence, with a considerable degree of certainty.

Although it lies a little outside our province, it is as well to mention the **Test Devised by Hijmans van den Bergh,** who contends that it is possible to distinguish hepatic from non-hepatic bilirubin in blood serum.

The following substances are required :—

(1) A solution composed of 1 part of sulphanilic acid, 15 parts of HCl, and 1,000 parts of distilled water.

(2) 0·5 per cent. solution of sodium nitrite.

These stock solutions are mixed in the proportion of 25 c.c. of (1) and 3 c.c. of (2) immediately before using.

The so-called *indirect reaction* is performed by mixing 1 part of serum with 2 parts of absolute alcohol ; the mixture is centrifuged and the fluid is drawn off with a pipette. The fluid is now mixed with $\frac{1}{4}$ part of the reagent, and a positive reaction is shown by the development of a red colour either immediately or within a few minutes.

The *direct reaction* is performed by mixing 1 part of serum with 2 parts of water and $\frac{1}{4}$ part of the reagent ; a red colour rapidly develops if the reaction is positive.

The direct reaction is of considerable value in the diagnosis of obstructive jaundice, but further information is still required with regard to the indirect one.

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Haden, R. L. *Journ. of Lab. and Clin. Med.*, 1923, lx.
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APPENDIX II

A VERY brief account of a considerable number of text-books and monographs is included in this section. No pretence at completeness is made, and apologies are tendered to those writers whose works have not been cited. They have been omitted solely because I am less well acquainted with their books as they do not, very unfortunately, form a part of my personal collection of hæmatological books, and therefore I cannot claim to have intimate acquaintance with their contents. In fact, only books reposing on my own shelves have been included in this Appendix.

Arneth, J. Die neutrophilen weissen Blutkörperchen bei Infektionskrankheiten. GUSTAV FISCHER, JENA, 1904. (*German.*) 200 pp. and 31 plates.

This was the first extensive publication dealing with Arneth's classification of leucocytes on the basis of their nuclear configuration.

Arneth, J. Die qualitative Blutlehre. Band I. und II., 1920. Band III., 1925. Band IV., 1926.

Over 1,000 pages devoted to descriptions of the changes in the leucocytes in every possible physiological and pathological condition. Probably this book represents the greatest sustained hæmatological labour ever undertaken.

Bezançon, P.; **Le Sourd**; **Agasse-Lafont**; **Pagniez**; **Hazard**; **Sainton et Apert.** Sang, Organes hematopoietiques, Rate, Os. A. MALOINE ET FILS., PARIS, 1922. (*French.*) 544 pp.

Boerner-Patzelt, D.; **Gödel, A.**; **und Standenath, F.** Das Retikuloendothel. GEORG THIEME, LEIPZIG, 1925. (*German.*) 124 pp.; extensive bibliography.

An excellent review of all the work on the structure and function of reticulo-endothelium.

Bond, C. J. The Leuocyte in Health and Disease. LEWIS, LONDON, 1924. 83 pp. and 24 plates.

An account of the reactions of leucocytes to a large variety of stimuli, particularly *in vitro*.

Bramwell, B. Anæmia and some of the Diseases of the Blood-forming Organs and Ductless Glands. OLIVER AND BOYD, EDINBURGH, 1899. 450 pp.

One of the last almost purely clinical text-books of hæmatology, and interesting as showing the position of the subject at the end of the last century.

Burnham, F. W. E. Hæmocytes and Hæmic Infections. Winnipeg, 1913. 462 pp. and 226 plates.

A book of great interest on account of its astonishing photomicrographs.

Cabot, R. C. A Guide to the Clinical Examination of the Blood for Diagnostic Purposes. Longmans Green & Co., London, 1904 (5th Ed.), 549 pp.

A general text-book, which is now rather out of date.

Coles, A. C. The Blood: How to Examine and Diagnose its Diseases. Churchill, London, 1905, 340 pp.

A text-book intended mainly for practitioners.

Cooke, W. E. The "Arneth" Count. Gilmour and Lawrence, Glasgow, 1914, 52 pp.

An account of a simplified modification of Arneth's original method, which has not been widely adopted, but is of some value to those unable to spare time for the more elaborate examination.

Da Costa, J. C. Clinical Hæmatology. Rebman, London, 1906, 591 pp. and 9 plates.

An excellent if old-fashioned account of hæmatology.

von Domarus, A. Methodik der Blutuntersuchung, mit einem Anhang Zytodiagnostische Technik. Springer, Berlin, 1921. (*German.*)

Every known method of blood examination is described in detail and a complete bibliography is appended.

Ehrlich, P.; von Noorden, K.; Lazarus, A.; and Pinkus, F. Diseases of the Blood (translated by A. Stengel). Saunders, Philadelphia and London, 1905, 715 pp.

This is a translation of a great hæmatological classic.

Ellermann, V. The Leucosis of Fowls and Leucemia Problems. Gyldendal, London, 1921, 105 pp. and 3 coloured plates.

A review of our knowledge of leucosis in fowls written by the first investigator to transmit the disease from one fowl to another.

Eppinger, H. Die Hepato-lienalen Erkrankungen. Springer, Berlin, 1920. (*German.*) 610 pp.

The most notable contribution to the literature of diseases affecting the liver and spleen; contains a brief account of diseases of the spleen by H. Hirschfeld, and an account of splenic surgery by E. Ranzi.

Evans, F. A. Pernicious Anæmia. Baillière, Tindall and Cox, London, 1926, 178 pp.

An account of the theory that the essential features of the disease lies in a defect of anti-hæmolytic lipoids.

Ferrata, A. Hæmatologica. Jovene e c. Napoli (*Italian and other languages.*)

A periodical (7 volumes to 1926) on lines similar to the Folia Hæmatologica, but mainly representative of Italian thought.

Ferrata, A. Le Emopatie, Vol. I., 1918 (out of print). Vol. II., 1923. Societa Editrice Libraria, Milano. (*Italian.*)

The most excellent exposition of the Italian school of hæmatological thought; very beautifully illustrated.

Fiessinger, N. Les Ferments des Leucocytes. Masson et Cie, Paris, 1923. (*French.*) 233 pp. Excellent bibliography.

The only monograph devoted to the subject of leucocytic enzymes, of which it gives a most comprehensive account.

Fischer, H. Myeloische Metaplasie und fötale Blutbildung. Springer, Berlin, 1910. (*German.*) 140 pp.

A monograph devoted to the discussion of the mode of occurrence of myeloid metaplasia; it is based almost entirely on personal observations.

Foa, P. Sangue e Organi ematopoetici. Unione Tipografico, Torino, 1921. (*Italian.*) 204 pp.

A general account, which follows usual lines, but is valuable because more space is given to the hæmatopoietic organs and less to the blood than is usual. Bibliography small, and pictures rather poor.

Fuller, A. W. Anæmia: its Causes and Modern Treatment. Lewis, London, 1923, 63 pp.

An example of a purely clinical account of anæmia in a form almost completely foreign to modern hæmatological opinions.

Gilbert, A., and Weinberg, M. Traite du Sang, Vol. I., 1913; Vol. II., 1921. Baillière, Paris. (*French.*) 698 and 695 pp. respectively.

Only the first volume deals with morphological hæmatology, and is written by a large number of collaborators. Apart from the completeness of the account of French hæmatological thought there is little in the book.

Gordon, A. Knyvett. Hæmatology in General Practice. Baillière, Tindall and Cox, London, 1923, 98 pp. and 1 coloured plate.

A small guide intended to indicate to the practitioner in what types of cases hæmatological examination may be of immediate value.

Gruner, O. C. The Biology of the Blood-cells. Wright, Bristol, 1913, 392 pp. and 7 plates.

An extensive account of hæmatology based on Pappenheim's views. It is, in places, almost as difficult to read as are Pappenheim's own writings.

Di Guglielmo, G. Le porpore emorragiche. Coi tipi della Tipografia Co-operativa, Pavia, 1926. (*Italian.*) 149 pp.

Excellent accounts of Werlhof's disease and of symptomatic purpural. Bibliography good. The monograph is valuable as showing the confusion which can arise as the result of trying to fit in every synonym that has ever been employed.

Hammar, J. A. Die Menschenthymus. Teil I. Akademische Gesellschaft, Leipzig, 1926. (*German.*) 570 pp., 20 charts. Admirable bibliography.

A summarised presentation of the anatomy of the thymus, to the study of which the author has devoted so many years. Part II. is not yet published.

Hayem, G. Leçons sur les modifications du sang sur l'influence des agents medicamenteux et des pratiques therapeutiques. Masson, Paris, 1882. (*French.*) 540 pp.

An account of the first systematic attempts at establishing hæmatological therapeutics on a sound experimental basis.

Hayem, G. Du Sang et de ses alterations anatomiques Masson, Paris, 1889. (*French.*) 1035 pp.

The first detailed text-book of clinical hæmatology.

Helly, K. Die hämatopoetischen Organe in ihren Bezichungen zur Pathologie des Blutes. Hölder, Wien, 1906. (*German.*) 205 pp. and 1 coloured plate.

An excellent account of hæmatology in which the changes in the formative organs are discussed at greater length than are the alterations in the blood.

Henke und Lubarsch. Handbuch der speziellen pathologischen Anatomie und Histologie. Band I., Teil I., 1926. Springer, Berlin, 1926. (*German.*)

Blut bei C. Sternberg, Wien ; Fremde Blutbeimengungen bei Huebschmann of Düsseldorf ; Die Malaria bei Seyfarth of Leipzig ; Die Lymphknoten bei C. Sternberg of Wien ; Lymphomatosis granulomatosa bei E. Fraenkel of Hamburg.

A part of the enormous system which is being edited by Henke and Lubarsch ; it is scarcely as compendious as had been hoped by many.

Herz, A. Die akute Leukämie. Deuticke, Wien. 1911. (*German.*) 184 pp. and good bibliography.

A very complete account of the acute leucoses.

Hirschfeld, H. Lehrbuch der Blutkrankheiten. Hirschwald, Berlin, 1918. (*German.*) 230 pp. and 7 coloured plates.

The best short account of clinical hæmatology presented with a minimal but sufficient consideration of theory.

Hunter, W. K. Recent Advances in Hæmatology. Henry Kimpton, London, 1911. 119 pp. and 1 coloured plate.

A series of lectures dealing mainly with the position of clinical hæmatology at the time of publication.

Jolly, J. Traite technique d'hematologie. A. Maloine et Fils, Paris, 1923. (*French.*) 1131 pp., 699 figures in text, and 1 plate.

There is no other book covering the same ground. Hæmatological technique as applied to lower animals as well as to man is dealt with in detail, and throughout the book the comparative anatomical aspect of hæmatology is kept in the foreground. The amount of space devoted to pathological hæmatology is small. Many literary references.

Keynes, G. Blood Transfusion. Henry Frowde and Hodder and Stoughton, London, 1922. 166 pp. and admirable bibliography.

A valuable review of modern knowledge and methods.

Klein, St. Die Myelogonie (als Stammzelle der Knochenmarkszellen im Blute und in den blutbildenden Organen und ihre Bedeutung unter normalen und pathologischen Verhältnissen). Springer, Berlin, 1914. 140 pp. and 10 coloured plates.

The whole of this monograph is devoted to explaining and supporting the writer's contention that a cell, which is the ancestor of both granulocytes and red cells (myelogonium), can be found in the bone marrow.

Kraus, F., und Brugsch, Th. Spezielle Pathologie und Therapie innerer Krankheiten. Band VIII., 1920. Urban und Schwarzenberg, Berlin. (*German.*)

A composite effort by Pappenheim, Naegeli, Ziegler, Hirschfeld Pinkus, Herz, Brugsch, Jágic, Mosse, Rosin, and Erich Meyer One of the most complete accounts of the morphology of the blood in disease.

Labadie-Lagrave. Traité des Maladies du Sang. Vigot Frères, Paris, 1904. (*French.*) 730 pp.

For long the standard French text-book of hæmatology.

Lazarus, A. Die Anæmie. Alfred Hölder, Wien. 1913. (*German.*) 256 pp. and 2 plates.

This is the second edition of the classical account of anæmias which was issued, in its first edition, by Ehrlich.

Lazarus, A., und Naegeli, O. Die Anæmie (Normale und pathologische Histologie des Blutes). Hölder, Wien, 1909 161 pp. and 5 plates.

This is the second edition of a book which was written, in its first edition, by Ehrlich.

Limbeck, R. R. The Clinical Pathology of the Blood (translated by Latham). New Sydenham Society, London, 1901. 338 pp.

A valuable classic.

McGowan, J. P. Pernicious Anæmia, Leucæmia and Aplastic Anæmia. Lewis, London, 1926. 116 pp.

One of the most original monographs published. The author deals with the various diseases as illustrated by the leucoses of fowls, of which he has great experience.

Meulengracht, E. Der chronische hereditäre hämolytische Ikterus. Werner Klinkhardt, Leipzig, 1922. (*German.*) 226 pp. Extensive bibliography.

The most complete monograph dealing with familial acholuric jaundice.

Moynihan, B. The Spleen and Some of its Diseases. John Wright and Sons, Bristol, 1921. 129 pp. and 13 plates.

An interesting account of diseases of the spleen from the surgical aspect without very much new information, but with an admirable correlation of modern knowledge.

Naegeli, O. Leukæmie und Pseudoleukæmie. Holder, Wien. 1913. (*German.*) 226 pp. and 8 plates.

The first edition of this classic was written by Ehrlich, Lazarus and Pinkus.

Naegeli, O. Blutkrankheiten und Blutdiagnostik. 4th Ed. Springer, Berlin, 1923. (*German.*) 587 pp. and 25 coloured plates. Good bibliography.

Probably the most complete text-book of clinical hæmatology, and is not confined entirely to immediately practical problems, but gives a most admirable survey of the whole subject. The characters of changes in the circulating blood are given much more attention than are the alterations of the formative organs.

Heim Pal es Preisich Kornel. Altalanos hæmatologia. Tar-

SULAT SAJATJA, BUDAPEST, 1908. (*Magyar.*) 168 pp. and 4 coloured plates.

The only text-book of hæmatology in the Magyar language. An excellent brief review of the subject in modern form.

Pappenheim, A. Atlas der menschlichen Blutzellen. GUSTAV FISCHER, JENA, 1909. (*German.*) 42 coloured plates.

This is by far the most beautiful atlas of blood-cells in existence.

Pappenheim, A. Folia Hæmatologica. WERNER KLINKHARDT, LEIPZIG.

This periodical, which was founded and edited by Pappenheim, has been edited by Naegeli and Downey since the death of the founder. It is published in two parts : the one (Archiv.) contains only original papers (thirty-two volumes have been published up to 1926) ; and the second part (Zentral-Organ) contains classified abstracts of hæmatology in the widest sense of the word (twenty-two volumes have been published up to 1926). This periodical is a gold-mine of hæmatological information.

Pappenheim, A. Morphologische Hämatologie. WERNER KLINKHARDT, LEIPZIG, 1919. (*German.*) 2 vols., 766 and 264 pp., 10 beautiful coloured plates.

This is the posthumously published *magnum opus* of the great hæmatologist, and was prepared for publication by Hirschfeld. The first volume deals with the cells of normal and pathological blood in a most comprehensive manner. The second volume, which unfortunately was incomplete at the time of the author's death, discusses the genesis of blood-cells. Like many of the author's other writings, it is often difficult to follow the argument, but the two volumes contain a monumental amount of information.

Pappenheim, A. Die Zellen der leukämischen Myelose. FISCHER, JENA, 1914. (*German.*) 202 pp., 20 beautiful coloured plates illustrating almost every conceivable type of myeloid leucocyte. As an atlas the book has never been surpassed.

Pearce, R. M., Krambhaar, E. B., and Frazier, C. H. The Spleen and Anæmia. LIPPINCOTT CO. PHILADELPHIA and LONDON, 1917.

A wonderful review of experimental work.

Petri, S. Undersogelser over Wright's Blodpladeteori. LEVIN AND MUNKSGAARD, KOBENHAVN, 1926. (*Danish.*) 243 pp. and 8 coloured plates.

The most comprehensive consideration of the blood platelets and megakaryocytes, in which the author reaches the conclusion

that Wright's theory of the genesis of platelets from megakaryocytes in the bone marrow is incorrect.

Pittaluga, G. Enfermadades de la Sangre. CALPE, MADRID. 1922. (*Spanish.*) 622 pp., 4 fair coloured plates. Some bibliography.

An excellent introduction to clinical hæmatology, but covers approximately the same ground as Ferrata, whom the writer seems to follow even in details.

Price-Jones, C. Blood Pictures. WRIGHT & SONS, BRISTOL. 1920. 64 pp. and 5 plates.

A very brief and incomplete introduction to clinical hæmatology, which is enriched by the coloured plate indicating the author's views of the structure and genesis of blood cells.

Rieux, J. Traité d'hématologie clinique. DOIN, PARIS. 1924. (*French.*) 761 pp., 16 coloured plates.

An excellent modern French text-book in which the whole field of hæmatology is discussed together with many references to the parasitology of the blood. References to hæmatological literature are not numerous and are mainly French.

Roger, G. H., Widal, F., and Teissier, P.J. Affections du sang et des organes hématopoïétiques (being Vol. I. of the Nouveau Traité de Médicine.) MASSON ET CIE., PARIS, 1927. (*French.*) 802 pp. Numerous plates and figures.

This is a monumental composite work, and represents the most recent exposition of French thought.

Rosenow, G. Blutkrankheiten. SPRINGER, BERLIN. 1925. (*German.*) 260 pp. and many text figures.

The most excellent introduction to hæmatology with which I am acquainted.

Schaumann, O. Zur Kenntniss der sogenannten Bothriocephalus-Anämie. WEILIN AND GÖÖS, HELSINGFORS, 1894. (*German.*) 214 pp. and 2 coloured plates.

The only monograph devoted to the description of Bothriocephalus anæmia, and, although getting old, is of great value.

Schilling, V. Das Blutbild und seine klinische Verwertung. GUSTAV FISCHER, JENA (6th Ed.), 1926. 292 pp. and 4 coloured plates.

A complete account of the author's method of classifying the neutrophilic leucocytes, and the application of the findings to diagnosis and prognosis.

Schittenhelm, A. Handbuch der Krankheiten des Blutes und der Blutbereitenden Organe (2 vols.). SPRINGER, BERLIN, 1925. (*German.*) Vol. 1, 616 pp. Very

numerous figures. Excellent bibliography. Vol. II., 691 pp.

A list of the contents of the two volumes will indicate the enormous scope of this monumental work, which well deserves to become a hæmatological classic: General Embryology, Morphology and Biology of the Blood Cells and Hæmatopoietic Organs, by O. Naegeli, of Zürich; Pathological Physiology of the Blood, by M. Bürger, of Kiel; Symptomatic Blood Changes, by H. Hirschfeld, of Berlin; Leukæmia and Allied Conditions, by H. Hirschfeld, of Berlin; Secondary Anæmia and Chlorosis, by M. Bürger, of Kiel; Pernicious Anæmia, by the late O. Schaumann, of Helsingfors, and F. Saltzmann, of Helsingfors; Polycythæmia, by H. Hirschfeld, of Berlin; Hæmorrhagic Diatheses, by E. Frank, of Breslau; The Morphology of the Reticulo-endothelial System, by L. Aschoff, of Freiburg; Normal and Pathological Physiology of the Reticulo-endothelial System, by A. Schittenhelm, of Kiel; Clinical Aspect of the Reticulo-endothelial System, by A. Schittenhelm, of Kiel; Hæmophilia, by E. Wöhlisch, of Berlin; Paroxysmal Hæmoglobinuria, by F. Schellong, of Kiel; Hæmatoporphyria, by H. Günther, of Leipzig.

Schmidt, Viggo. Zur Tonsillenfrage: Klinische und hämatologische Untersuchungen. Kabitsch, Leipzig, 1926. (*German.*) 83 pp.

Interesting as showing how much new information can be obtained by serial examinations of the blood in common maladies.

Sheard, A. A Contribution to the Study of Pernicious Anæmia. Wright and Sons, Bristol, 1923. 94 pp.

A thesis based on the study of fifteen cases of the disease.

Sternberg, C. Pathologie der Primärerkrankungen des lymphatischen und hämatopœtischen Apparates. Bergmann, Wiesbaden, 1905. (*German.*) 209 pp. and several plates (some coloured).

A general account of hæmatology with special reference to the leukæmias.

Türk, W. Vorlesungen über klinische Hæmatologie. 3 Vols. Braumuller, Wien und Leipzig, 1904–1912. (*German.*) 402, 410, and 1012 pp.

A classical series of lectures, from which, however, the most important parts have appeared in many newer and smaller books.

Vasiliu, T. Sangele si organele hematopoietice hematologia. Institutul de arte grafice. Ardealul, Cluj, 1923. (*Roumanian.*) 528 pp. and 3 beautiful plates.

A most complete text-book in which Ferrata's views are followed, although the writer gives scope to his own conceptions in many places. Were it not for the difficulty of the language, it is probable that this would become a standard work on the subject.

Wanner, F. Hematologie clinique. A. Maloine et Fils, Paris, 1924. (*French.*) 196 pp., 8 coloured plates.

A small book for students and practitioners of a type badly needed in English, as it gives an excellent general survey of pathological hæmatology.

Weber, F. P. Polycythæmia, Erythrocytosis, and Erythræmia. Lewis, London, 1921. 148 pp. and very large bibliography.

The most complete monograph on the subject.

Weidenreich, F. Die Leucocyten und verwandte Zellformen. Bergmann, Wiesbaden, 1911. (*German.*) 415 pp. and 3 coloured plates.

The most detailed account of the comparative histology of the leucocytes together with the most rigidly monophyletic interpretation of the facts. Many literary references.

Weissenbach, R. J. Les Syndromes anémiques et leur traitement. Doin, Paris, 1924. (*French.*) 372 pp.

Excellent summary of French work.

Zibordi, F. Ematologia infantile normale e patologia. Instituto Editoriale Scientifico, Milan, 1925. (*Italian.*) 479 pp.

The only book devoted to the hæmatological problems of infancy ; an admirable reference work and full of stimulating suggestions.

Ziegler, K. Die Hodgkinsche Krankheit. Gustav Fischer, Jena, 1911. (*German.*) 204 pp. and 4 plates.

A most complete account of Hodgkin's disease in all its aspects.

Plate I.

(Reprinted from "The Principles of Hæmatological Differentiation." A. Piney. *Journal of the Royal Microscopical Society*, 1926.)

Fig. 1.—**Myeloblast.** The essential characters of the specific stem-cell of the myeloid series of leucocytes are well brought out, viz., pale basophilic protoplasm and the relatively palely staining nucleus. The nuclear characters are clearly drawn, and show the finely stippled structure, which does not become any denser at the edge of the nucleus, and, therefore, there is no sign of a nuclear membrane. The characters of this cell should be carefully compared with those of—

Fig. 2.—**Lymphoblast.** The cytoplasm differs in no way from that of the myeloblasts, but the nuclear characters are quite distinctive. The basi-chromatic stippling of the nucleus is much more distinct than is that of the myeloblasts, and the individual particles are distinctly coarser. At the edge of the nucleus the basi-chromatin tends to be collected into a fairly dense nuclear membrane.

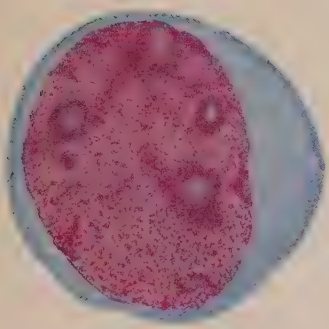
Fig. 3.—**Pro-Monocyte.** The cytoplasm is rather darker than is usually seen in these cells. The nucleus has the essential characters of the myeloblast, viz., fine basi-chromatic stippling, nucleoli, and absence of nuclear membrane. There is, even in this early stage of the development of the monocyte, a difference between its nucleus and that of the myeloblast, viz., in the left-hand side of the nucleus there is a distinct tendency for the basi-chromatic particles to be arranged into fine threads such as are characteristic of the monocytic nucleus (*cf.* Plate II., Figs. 7 and 8).

Fig. 4.—**Neutrophilic Premyelocyte.** The nuclear characters of this cell are very similar to those of the myeloblast, but the nucleoli are smaller. The cytoplasm is in process of becoming slightly eosinophilic, and an almost full complement of granules is present. This stage of development lies on the genetic line between myeloblast and myelocyte, but the cell illustrated is more nearly allied to the myelocyte than to the myeloblast.

Fig. 5.—**Neutrophilic Metamyelocyte.** Here the cytoplasm is slightly but definitely eosinophilic, and a full complement of granules is present. The nucleus, which shows a clear distinction between basi- and oxy-chromatin, is somewhat indented, but there is as yet no true lobulation. It is obvious that this cell-type is intermediate between the myelocyte with typically round nucleus and the polymorphonuclear leucocyte with true lobulation.

Fig. 6.—**Neutrophilic Polymorphonuclear Leucocyte.** This is the form of neutrophilic granular leucocyte which is most numerous in normal blood, but, of course, the number of lobes may be greater or less than three. There is even less variability in the staining reaction of the granules of this cell than in the case of the metamyelocyte.

PLATE I



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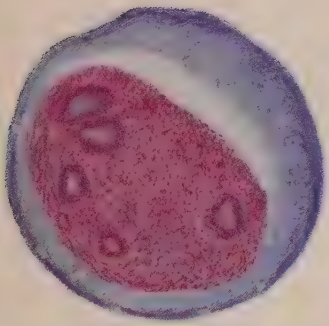

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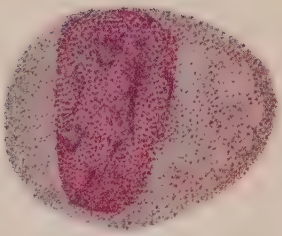

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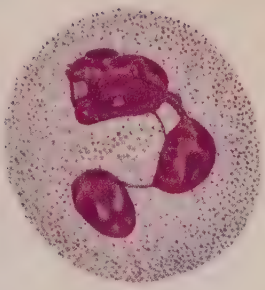

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Plate II.

(Reprinted from the same source as Plate I.)

Figs. 7 and 8.—**Monocytes.** The grey-blue protoplasm and the very finely-drawn nuclear basi-chromatin are very characteristic. The lobulation of the nucleus would bring the cells illustrated into Ehrlich's class of "transitional" leucocytes; but this term is no longer needed, because it is admitted that the shape of the nuclei of these cells is of no direct importance in their classification.

Fig. 9.—**Monocyte.** This cell has been slightly overstained with Giemsa's solution, which process intensifies the grey colour of the protoplasm, although it also obscures the finer nuclear detail. The method does, however, show the essentially granular character of the protoplasm, and here the very numerous azurophilic granules are clearly seen.

Fig. 10.—**Eosinophilic Premyelocyte.**—The nucleus has many of the characters of that of the myeloblast (*cf.* Figs. 1 and 4). The cytoplasm is still basophilic, but to a less degree than that of the myeloblast. The granules are irregular in size and are not yet truly eosinophilic. This cell represents a stage between the pre-eosinophilic premyelocyte and the true eosinophilic premyelocyte.

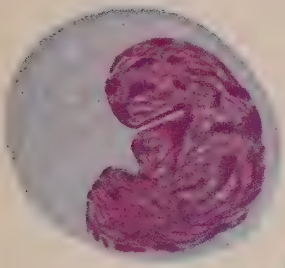
Fig. 11.—**Eosinophilic Polymorphonuclear Leucocyte.** This is the type of eosinophilic granular cell which is found in the normal circulation. The nuclear lobulation is rarely as sharp as that of the neutrophilic polymorphonuclear cells, and the basi-chromatin also usually stains a rather less intense shade of blue, *i.e.*, it is blue rather than purple.

Fig. 12.—**Basophilic Myelocyte.** The extreme basophilia of the cytoplasm, which is characteristic of the less mature stages, has almost disappeared, and a number of basophilic granules are present. The nucleus, which stains even less intensely than that of the eosinophilic granular cells, shows no sign either of bending or of lobulation.

Fig. 13.—**Small Lymphocyte.** This cell shows very clearly the poor demarcation of basi- from oxy-chromatin in lymphatic cells. The cytoplasm is rather more bulky and more basophilic than normal, and the appearances are those of a lymphocyte which is intermediate between the typical form and the so-called *Türk cell*.

Fig. 14.—**Lymphocyte.** This cell shows more distinct arrangement of the chromatin in a radiate manner. Such "cart-wheel" lymphocytes presumably represent a stage in the development of plasma cells.

PLATE II



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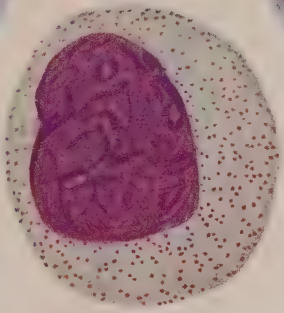

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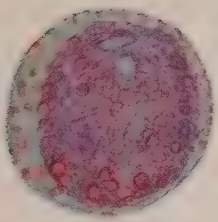

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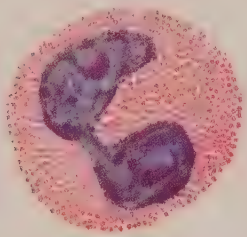

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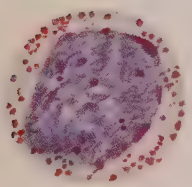

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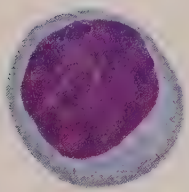

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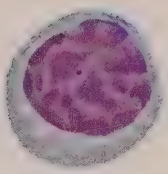

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Plate III.

Figs. 1 to 11.—Megaloblasts from the blood of cases of pernicious anæmia.

Fig. 1 shows the youngest form of megaloblast, which bears a close resemblance to the myeloblast, but it will be noticed that there is a fairly definite nuclear membrane, as in the lymphoblast, whereas the basi-chromatic stippling is as fine as that of the myeloblast.

Fig. 2 shows the early development of hæmoglobin (as indicated by eosinophilia of the cytoplasm) around the nucleus.

Figs. 3, 4 and 5 show typical young megaloblasts with finely stippled nuclei and protoplasmic polychromasia.

Figs. 6 and 7 show rather different forms of megaloblasts, but even here there is no tendency for the nuclear arrangement to be radial.

Fig. 8 shows a more mature megaloblast in which the nuclear arrangement is rather that of fine threads of basi-chromatin than of stippling. The protoplasm is obviously slightly eosinophilic, *i.e.*, hæmoglobiniferous.

Figs. 9 and 10 show various degrees of pyknosis and concomitant increase of hæmoglobin in the protoplasm.

Fig. 11 shows a gigantoblast which has all the typical characters of the megaloblast, although it is so much greater in size.

Figs. 12 to 16 show various types of macro-normoblast, which all show evidence of immaturity, viz., radiate arrangement of the nuclear chromatin and basophilia of the protoplasm.

Fig. 17 shows that, even when such a cell loses its nucleus by pyknosis and subsequent karyorrhexis and karyolysis, which is always a pathological phenomenon, it does not first become hæmoglobiniferous.

PLATE III

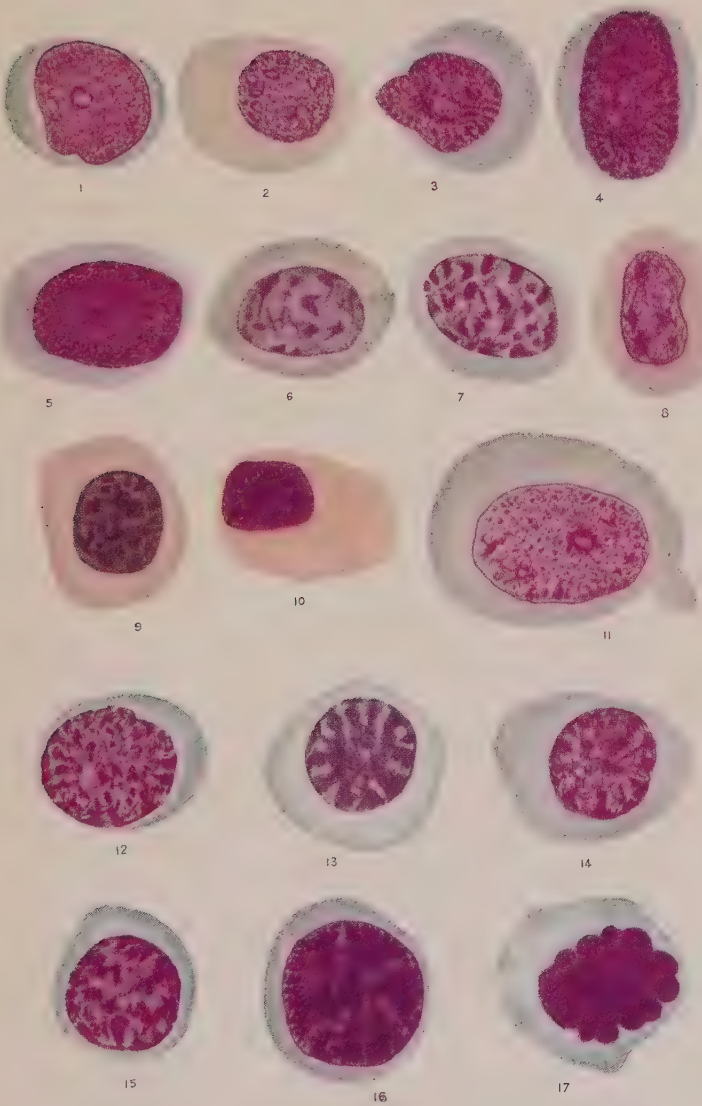
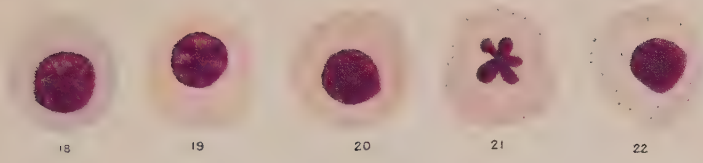


Plate IV.

Figs. 18 to 22 (reprinted from the *Journal of Pathology and Bacteriology* 1924) show ordinary normoblasts in various stages of maturation.

Fig. 23 (reprinted from the *British Journal of Surgery*, 1922).—A mass of epithelial cells is seen lying in an obvious blood channel. The illustration was prepared from a direct coloured photograph on a Lumière plate. It seems to supply clear evidence of the hæmatogenous origin of metastases in bone marrow.

PLATE IV



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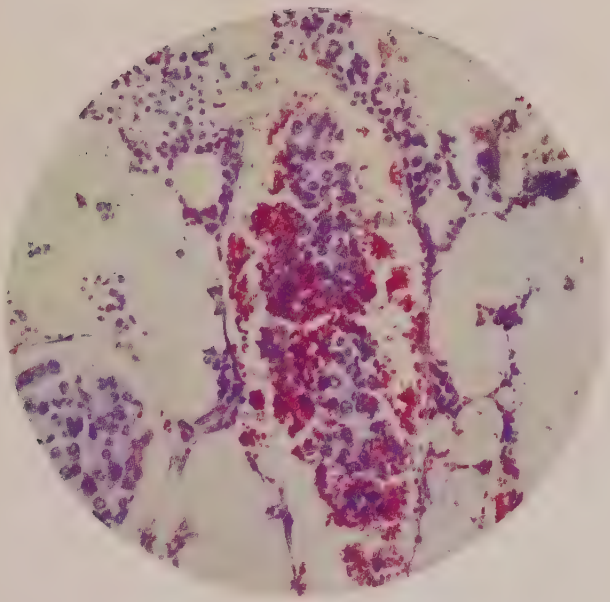

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